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PATHOGENESIS OF CIRRHOSIS OF THE LIVER OCCURRING IN PATIENTS WITH DIFFUSE TOXIC GOITER

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NEW YORK

FROM THE standpoint of morphology, the liver has received abundant attention in fatal cases of diffuse toxic goiter. The lesions found are various; there are fatty changes, parenchymatous degeneration, venous congestion and, finally, cirrhosis of such a distinctive character as to be pathognomonic of this disorder. These lesions occur singly or in various combinations. In an appreciable percentage of cases no lesion of the liver is found. Acute yellow atrophy has been reported by Raab and Terplan,[1] Kerr and Rusk,[2] Zeldenrust and van Beek [3] and Beaver and Pemberton.[4] Foci of necrosis have been reported by Beaver and Pemberton,[4] Habán,[5] Rössle [6] and Cameron and Karuntaratne.[7] Whether focal necrosis represents an early or an abortive phase of acute yellow atrophy is questionable. Beaver and Pemberton found focal necrosis in 6.5 per cent of the livers of 107 patients afflicted with diffuse toxic goiter; in 5 patients the necrosis was of sufficient intensity to be deemed acute yellow atrophy. In my series of 31 cases, foci of necrosis were found in only 1, approximately 3 per cent. This

From the laboratories, Department of Pathology, the Mount Sinai Hospital.

1. Raab, W., and Terplan, C.: Morbus Basedowii mit subakuter Leberatrophie, Med. Klin. **19**:1154, 1923.

2. Kerr, W. J., and Rusk, G. Y.: Acute Yellow Atrophy Associated with Hyperthyroidism, M. Clin. North America **6**:445, 1922.

3. Zeldenrust, J., and van Beek, C.: Morphologischer und experimenteller Beitrag zur Pathogenese der Leberveränderungen bei Morbus Basedowi, Beitr. z. path. Anat. u. z. allg. Path. **103**:568, 1939.

4. Beaver, D. C., and Pemberton, J. deJ.: Pathological Anatomy of the Liver in Exophthalmic Goitre, Ann. Int. Med. **7**:687, 1933.

5. Habán, G.: Ueber die Leberveränderungen bei Morbus Basedowii mit besonderer Berücksichtigung der Lebercirrhose, Beitr. z. path. Anat. u. z. allg. Path. **92**:88, 1933.

6. Rössle, R.: Ueber die Veränderungen der Leber bei der Basedowschen Krankheit und ihre Bedeutung für die Entstehung anderer Organsklerosen, Virchows Arch. f. path. Anat. **291**:1, 1933.

7. Cameron, G. R., and Karuntaratne, W. A. E.: Liver Changes in Exophthalmic Goitre, J. Path. & Bact. **41**:267, 1935.

necrosis was associated with cirrhosis typical of that found in cases of diffuse toxic goiter, but topographically the two lesions were independent. Other observers of cirrhosis in cases of diffuse toxic goiter do not report focal necrosis. Apparently focal necrosis is a rather unusual finding, and my reason for commenting on it is that some physicians regard the cirrhosis as arising from necrotic foci. I do not agree with this point of view.

In this study I shall be concerned only with a consideration of the cirrhosis.

Although disturbances of hepatic function play only a subordinate role in cases of diffuse toxic goiter, the study of the pathogenesis of this peculiar type of cirrhosis is of interest not only for its own sake but also for the important implications which it bears concerning the mechanism of some of the clinical cardiovascular disturbances commonly found in patients with diffuse toxic goiter.

HISTORICAL REVIEW

One of the earliest reports of cirrhosis occurring in patients with diffuse toxic goiter is that of Marine and Lenhardt,[8] who found atrophic cirrhosis in 4 of 6 patients; in all 4 the "exophthalmic goiter" was of long standing. They found small livers, sometimes smooth, sometimes slightly granular or distinctly hobnailed. The connective tissue content was increased and varied from slight thickening of the portal spaces to well marked fibrous bands. In 1930 Warthin,[9] in a study of the hepatic lesions in cases of "exophthalmic goiter," found in some instances a peculiar form of parenchymatous hepatitis, characterized by lymphocytic infiltration, bile duct proliferation and an increase of the connective tissue stroma of the portal spaces sufficient in his eyes to make the diagnosis atrophic cirrhosis. Warthin recognized that the lesion differs from the typical Laennec cirrhosis in that the new connective tissue is intralobular and irregularly distributed. Attention was first sharply focused on the cirrhosis in cases of diffuse toxic goiter by Rössle's[6] publication in 1933. Since then publications of studies of this lesion have been more numerous. Rössle ascribed the pathogenesis of the cirrhosis to "serous hepatitis" of toxic origin, a lesion which he had described many years before[10] as the essential primary phenomenon of the conventional type of Laennec cirrhosis. The lesion begins with accumula-

8. Marine, D., and Lenhardt, C. H.: Pathological Anatomy of Exophthalmic Goitre, Arch. Int. Med. **8**:265 (Sept.) 1911.

9. Warthin, A. S.: Hepatic Lesions Associated with Exophthalmic Goitre, Ann. Int. Med. **4**:501, 1930.

10. Rössle, R.: Die Veränderungen der Blutkapillaren der Leber und die Bedeutung für die Histogenese der Lebercirrhose, Virchows Arch. f. path. Anat. **188**:484, 1907.

tion of fluid in the Disse spaces, a pericapillary edema, with disintegration of the capillaries, resulting in hyperemia and occasional hemorrhages or formation of "blood lakes"; there is disassociation of the liver cells, which may be vacuolated or may stain faintly. In the later phases new collagenous fibrils are laid down in the Disse spaces. Rössle did not regard this new formation of fibrils as inflammatory, because it occurs without the intermediacy of granulation tissue, and he cited in explanation the work of Doljanski and Roulet,[11] who found that in cultures of cells collagenous fibrils were deposited in the plasma far away from the new cellular formation. In the further development of the cirrhotic process the new connective tissue increases and encloses smaller or larger fragments of hepatic trabeculae, which often undergo new bile duct formation. In this concept the capillary toxicosis is primary and the changes in the parenchyma are secondary. Rössle correctly emphasized the striking predilection of the process for the subcapsular areas of the liver. He ascribed this predilection to the fact that toxic substances are more liable to affect this region and cited the observation of Laird,[12] who injected sodium iodide and phosphorated oil into the portal vein and found these substances most abundant in the subcapsular region.

Habán in the same year [5] reported cirrhosis in 10 of 26 patients who died of "Basedow's disease." Like Rössle, he found the increase of connective tissue most marked beneath the capsule, from which strands penetrate the parenchyma to a greater or lesser extent. He found accretion of connective tissue only rarely in other areas of the organ. He noted the angiomatous dilatation of the vessels and the islets of liver cells within the cirrhotic areas, which may undergo bile duct transformation. The new connective tissue conspicuously differs topographically from that noted in Laennec cirrhosis in that the areas are star shaped and do not intercommunicate. The new connective tissue varies in the degree of cellularity and includes mostly lymphocytes, occasionally plasma cells and a few polymorphonuclear leukocytes. He viewed the genesis as connective tissue replacement of previous necrosis. He offered no explanation for the subcapsular predilection.

Weller [13] also in 1933, in a study of the hepatic changes in cases of "exophthalmic goitre," found patchy parenchymal interlobular hepatitis in 26 of 48 cases, characterized by lymphocytic infiltration, bile duct formation and increased stroma in the capsule of Glisson. He noted

11. Doljanski, L., and Roulet, F.: Studien über die Entstehung der Bindegewebsfibrille, Virchows Arch. f. path. Anat. **291**:260, 1933.

12. Laird, E. G.: Peritoneale Resorption mit besonderer Berücksichtigung der Wirkung auf die Leber und die Resorptionswege zur Leber, Virchows Arch. f. path. Anat. **291**:440, 1933.

13. Weller, C. V.: Hepatic Lesions Associated with Exophthalmic Goitre, Tr. A. Am. Physicians **45**:71, 1930; Hepatic Pathology in Exophthalmic Goiter, Ann. Int. Med. **7**:543, 1933.

that many of the portal spaces were intact and that there was an intralobular connective tissue invasion of the periphery of the lobules—attributes that differentiated this form of cirrhosis from the Laennec type. He regarded the lesion as toxic and not cardiac because the new connective tissue was not around the central veins.

Beaver and Pemberton [4] in 1933-1934 reported the hepatic changes in 107 fatal cases. They found two outstanding types of changes: (1) acute, characterized by fatty metamorphosis and central and focal necrosis; (2) chronic, which is again subdivided into (*a*) simple atrophy and (*b*) toxic subacute atrophy which in some instances progressed to actual cirrhosis. They attached little importance to the fatty changes because such changes occur in a wide variety of other conditions, although to an appreciably less degree than in diffuse toxic goiter. The livers that showed simple atrophy without cirrhosis showed little; but significantly, to me at least, the authors described streaks or bands of connective tissue within the lobule, around the periportal spaces or extending between two periportal spaces. They regarded these changes as the result of simple parenchymal atrophy, possibly of degeneration, but their findings resemble so closely, topographically at least, those found in my cases that they might be regarded as already representing early cirrhosis. Beaver and Pemberton reported 64 cases of cirrhosis, mild in 48 and severe in 16. Microscopically, they noted a variability of the localization of the new connective tissue. The largest amounts were around the periportal spaces, encroaching on the periphery of the lobule. In other instances the connective tissue occurred throughout the lobule or around the central veins or as threadlike bands extending between the central and the portal veins or between two portal spaces. The new connective tissue contained lymphocytes and new bile ducts. Regeneration was not a prominent feature. They regarded the genesis as toxic, in part the result of simple atrophy. The lesions revealed various grades; in most instances they were progressive, corresponding morphologically to subacute or early chronic toxic atrophy of the liver.

Cameron and Karuntaratne [7] in 1935 described three types of morphologic change in the liver in cases of "exophthalmic goitre": (1) acute damage (marked fatty change and/or foci of necrosis); (2) progressive damage (various stages of cirrhosis); (3) arrested damage (nodule formation, atrophy). Of 30 cases, 10 showed cirrhosis, in 3 of which the insular type, in 4 the interinsular type and in 3 the annular type was represented. The microscopic descriptions are so sketchy that one cannot determine the precise morphologic character of the lesions. Apparently, the insular type refers to a lesion in which there is lymphocytic infiltration of the portal spaces. Whether this change may be classified as cirrhosis is questionable. The interinsular and the

annular types represent the characteristic cirrhosis of diffuse toxic goiter. The authors submitted no explanation of the pathogenesis. Zeldenrust and van Beek [8] reported a case in 1939. The cirrhosis was mostly subcapsular; there was venous congestion; the endothelium of the hepatic capillaries was loosened, and erythrocytes were found in Disse spaces. The authors viewed this "serous hepatitis" as secondary and not primary. They were the first to regard the genesis of the lesion as cardiac but submitted no reasons therefor.

Schaffer [14] in 1940, in a study of 24 cases of "hyperthyroidism," found cirrhosis in 6—advanced in 2 and moderate in 4. The cirrhosis was characterized by degenerative changes leading to atrophy of the hepatic cells and by a chronic inflammatory reaction occurring peripherally in the altered lobules, with regeneration of an imperfect type. Schaffer also noted "local interstitial hepatitis," characterized by lymphocytic infiltration of the periportal areas, in 83 per cent of the cases. In a control series he found identical changes in about 25 per cent. He did not regard the lesion as cardiac in origin.

OBSERVATIONS IN THIRTY-ONE CASES OF DIFFUSE TOXIC GOITER

Incidence of Cirrhosis.—Of 31 patients who died in Mount Sinai Hospital between the years from 1930 to 1944 and whose disease was diagnosed as diffuse toxic goiter, or exophthalmic goiter, during life, 11 had cirrhosis—an incidence of 35.5 per cent. This accords with 38.8 per cent found by Habán [5] in 26 cases of "exophthalmic goitre."

Sex Distribution of Cirrhosis.—Of the livers showing cirrhosis, 5 were from males and 6 from females. Of the total of 31 patients who died with the diagnosis of exophthalmic goiter, 20 were females and 11 males. The percentage of males with cirrhosis is higher than that conventionally regarded as the average. The significance of this difference is not apparent at this time.

Duration of the Syndrome.—As diffuse toxic goiter is a hyperkinetic disease,[15] it is sometimes difficult to judge the precise duration. This can be gaged with fair accuracy when the disease follows a sudden emotional crisis, but in most instances the onset is gradual, so that the patient's statement is only roughly approximate. Despite these shortcomings, it is apparent that, by and large, the incidence of cirrhosis bears a relation to the duration of the disease. Of 10 patients with cirrhosis from whom a history of the duration of the disease was

14. Schaffer, J. M.: Disease of the Liver in Hyperthyroidism, Arch. Path. **29**: 20 (Jan.) 1940.

15. Moschcowitz, E.: The Hyperkinetic Diseases, Am. J. M. Sc. **206**:576, 1943.

obtained, all but 2 revealed a duration of two years or more. In 5 patients the duration was between three and ten years. One stated that the duration was "over one year," and another that it was "more than two years." One said that the disease had lasted for "many years." Only 2 patients had been aware of the syndrome for less than one year.

Of the 20 patients without cirrhosis, 3 did not mention the duration of the disease, and 12 had been affected for a year or less. Two others had been cured of their thyroid malady by thyroidectomy ten years previously; one of these died of congestive failure due to coronary disease and the other of peritonitis following perforation of an ulcer of the sigmoid flexure. One of the remaining 3, all of whom presented evidences of diffuse toxic goiter both clinically and anatomically (as manifested by hyperplasia of the thyroid gland), died of congestive failure due to hypertensive disease; 2 revealed coronary arteriosclerosis and chronic congestion of the viscera, and died in "thyroid storms." Although the figures are only approximate, the average duration of the syndrome was three and a half years in patients with cirrhosis and eight months in those without cirrhosis. It is apparent that there is a definite relation between the duration of the disease and the incidence of cirrhosis. This is in accord with the experiences of Marine and Lenhardt,[8] Schaffer,[14] Cameron and Karuntaratne,[7] Beaver and Pemberton [4] and Habán.[5] However, the relation is not absolute since 2 of the patients with cirrhosis had diffuse toxic goiter one and four months, respectively, while 5 of those without cirrhosis had it for one or more years and 3 for five, eight and fourteen years, respectively. The reasons for the absence of cirrhosis will be discussed in a later portion of this communication.

Age.—It is noteworthy that in the postmortem experience at Mount Sinai Hospital the patients dying with evidence of diffuse toxic goiter have been mostly in the sixth decade of life. The average age of the 31 patients was 54.4 years; the youngest was 23 and the oldest 80 years of age. The average age of those in whom cirrhosis was revealed was 51.2 years; the youngest was 30 and the oldest 65. Of those without cirrhosis, the average age was 56.1 years; the youngest patient was 23 and the oldest 80. The difference between these two groups is not sufficient to be of significance.

This high age incidence, in my experience, can be ascribed first to the greater risk of operation in the older age group. The majority of these patients died after a postoperative "thyroid storm"; furthermore, a large number died during the years when preoperative administration of strong solution of iodine U. S. P. was not routine. A lesser number died of postoperative pneumonia. Second, cardiac failure following long-standing diffuse toxic goiter is exceedingly common during

the senescent years, as shown by the fact that about a third of these patients died with clinical and anatomic evidences of congestive failure.

Pathologic Changes in the Liver.—(*a*) Macroscopic Examination: The gross appearance of the livers which revealed cirrhosis varied, depending on the stage of the process. In the early phases the liver appears normal, with a smooth glistening capsule, and reveals firm consistency; the cut section shows the normal lobular structure, modified as the case may be by the presence and the intensity of fatty or parenchymatous degeneration or by venous congestion. In the later phases the surface of the liver may be granular or even nodular, a change involving the entire surface or, more commonly, circumscribed to one or more areas on either the superior or the inferior surface.

Fig. 1.—Gross appearance of the cirrhotic liver of a patient with diffuse toxic goiter, showing the subcapsular predilection of the fibrosis. This illustration is taken from Rössle.[6]

The capsule of the liver is sometimes appreciably thickened. The consistency of the organ is more dense, and it cuts with increased resistance. The cut surface reveals a trabeculated appearance, with nodules varying from 1 to 4 mm. in diameter and surrounded by firm fibrous tissue. Especially striking, as Rössle pointed out, is the prominence of these cirrhotic areas in the subcapsular zone; in 2 instances the process was limited strictly to this area (fig. 1). The weight of the liver averaged 1,200 Gm., varying between 890 and 1,800 Gm. According to Krieger,[16] the normal weight varies between 1,659 and 1,786 Gm. The diminution of size cannot be entirely

16. Krieger, M.: Ueber die Atrophie der menschlichen Organe bei Inanition, Ztschr. f. ang. Anat. **7**:87, 1920.

ascribed to the cirrhosis, since it is well known that patients with diffuse toxic goiter are usually below normal in weight and the weight of the liver decreases correspondingly. Inasmuch as sufficient data were not available in regard to the weights of the patients at death, I cannot say whether the weight of the liver as compared with the total body weight corresponds to the percentage, 2.69, which Krieger determined for the liver of the normal subject. Moreover, the weight of the liver is additionally modified by the amount of the contained blood, a congested liver weighing more than the average before the blood is expressed. As a matter of fact, the larger weights in the present series were those of livers in which venous congestion was associated.

The gross vessels of the liver did not reveal any abnormality. The gallbladder contained a calculus in 1 instance; it appeared normal in all other instances.

(*b*) Microscopic Examination: Superficial inspection reveals patches of fibrosis scattered apparently haphazardly throughout the hepatic lobule with no particular relation to any of the normal anatomic landmarks in the lobule, namely, the portal spaces or the central or the hepatic veins (fig. 2 *A*). These areas are usually wedge shaped and vary in size from those which occupy only a portion of a lobule to some that involve an entire lobule or a number of lobules. Often they are confluent and then they assume a stellate appearance (fig. 2 *B*). Within the larger areas apparently intact portal spaces are still visible. In accord with the macroscopic appearance, the subcapsular areas are predominantly involved, while the deep portions of the parenchyma are involved to an appreciably lesser extent. In a few instances the morbid changes were exclusively limited to the subcapsular area. Furthermore, the fibrotic areas are not scattered haphazardly but are often prolonged from the portal spaces either directly into the parenchyma of the lobule or, more commonly, directly into the vascular septums between the lobules. This intimate relationship between the portal spaces and the cirrhotic areas is confirmed in serial sections when one finds that a fibrotic area, apparently without demarcation, can be shown to arise from a neighboring portal space (fig. 3). The stellate areas of cirrhosis are the resultant of the projection from two or more portal spaces. Curiously, these areas of fibrosis arise usually from only the smaller divisions of the portal spaces, the larger ones being uninvolved. Not all the portal spaces are involved, and this is noted especially in the deeper portions of the parenchyma. When the fibrotic areas are followed peripherally from their origin in the portal spaces, many are seen to pass directly into the central vein or more commonly into the collecting veins (fig. 4) (*Sammelvene,* Pfuhl[17]). These collecting veins repre-

17. Pfuhl, W., in von Möllendorff, W.: Handbuch der mikroskopischen Anatomie des Menschen, Berlin, Julius Springer, 1932, vol. 5, pt. 2.

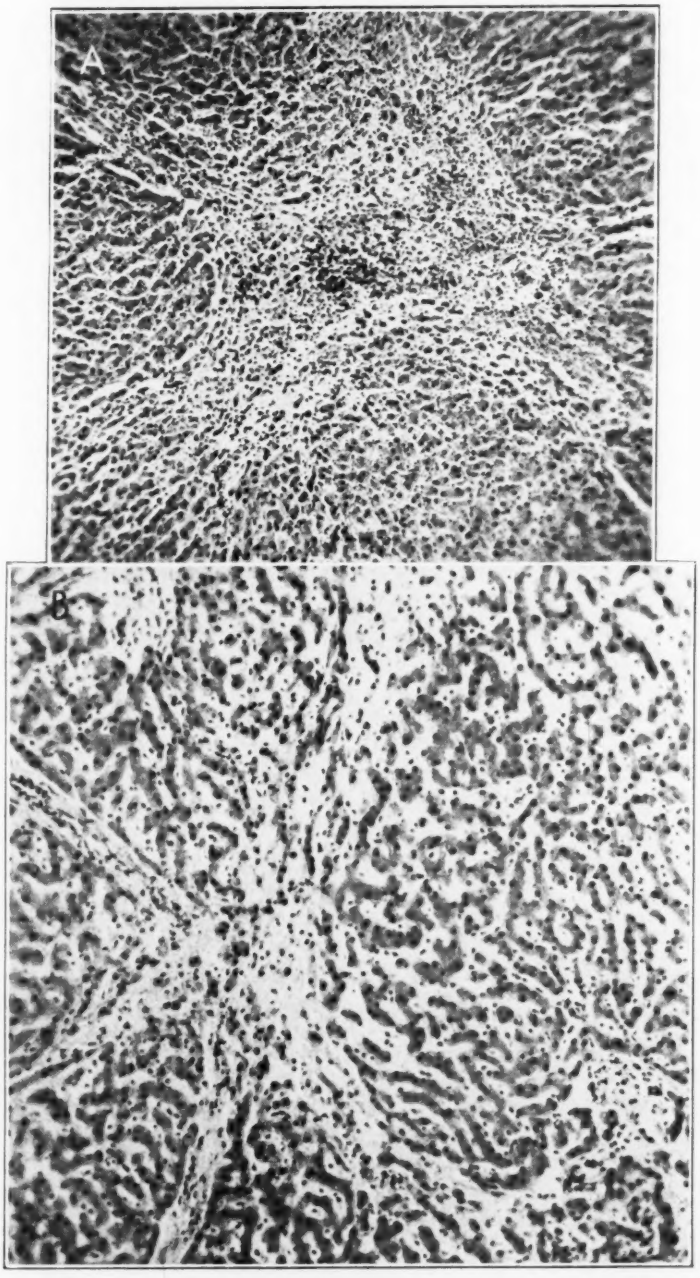

Fig. 2.—*A*, typical area of fibrosis apparently unrelated to any portal space, central vein or hepatic area. *B*, area of fibrosis presenting a stellate conformation.

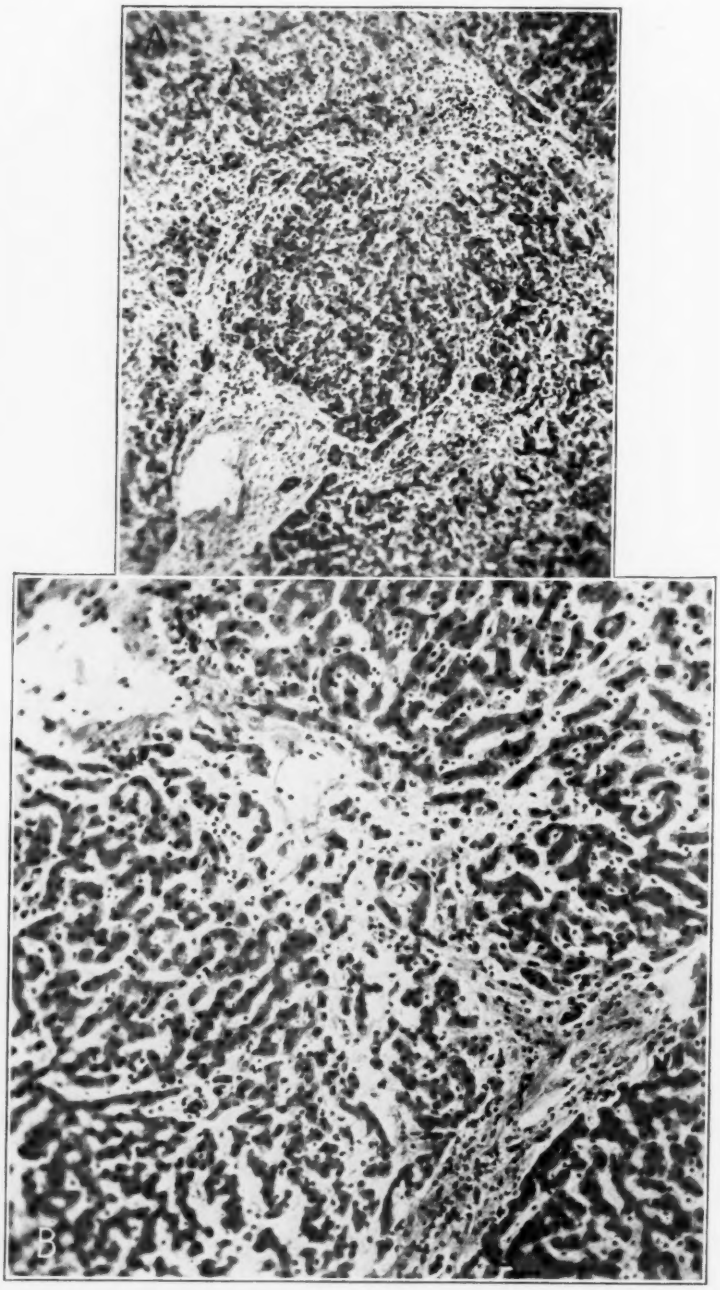

Fig. 3.—*A*, fibrosis arising from a small portal space and penetrating into interlobular spaces. *B*, terminal picture of serial sections showing fibrosis penetrating the central portion of a lobule and there breaking up into dilated sinusoids which end in a central or a collecting vein (*Sammelvene*).

sent the maturer forms of the central veins and are formed by the aggregation of a number of lobules into one unit, an arrangement which, according to Pfuhl (fig. 5), is the usual anatomic arrangement in the human liver.

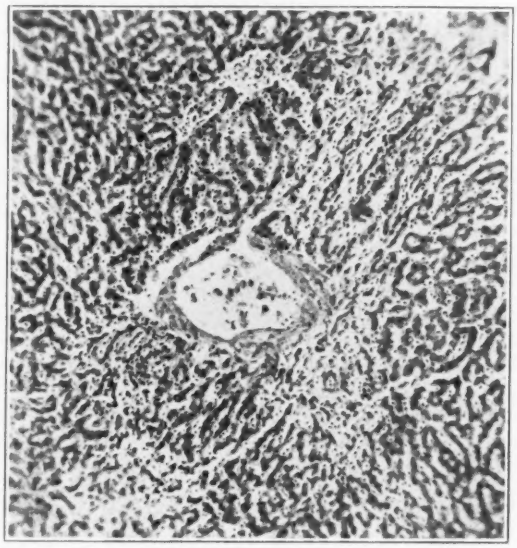

Fig. 4.—An area of fibrosis showing dilated sinusoids entering a central or a collecting vein (*Sammelvene*).

Fig. 5.—Scheme of a normal hepatic lobular cluster: *gr. P.*, large portal branch; *Vi.*, interlobular vein; *Lp.*, lobule; *C.*, central vein; *Sa.*, collecting vein (*Sammelvene*); *gr. L.*, large hepatic vein. (The scheme is taken from Pfuhl.[17])

I have not noted the complete encirclement of a lobule by the newly formed connective tissue so characteristic of Laennec cirrhosis. One notes at the most the isolation of a portion of the hepatic lobule.

The finer microscopic structure depends on the stage of the process. In the early phase the sinusoids are strikingly widened. The hepatic cell cords reveal more or less complete dissociation and consist of one or more cells embedded in a system of intercommunicating sinusoids

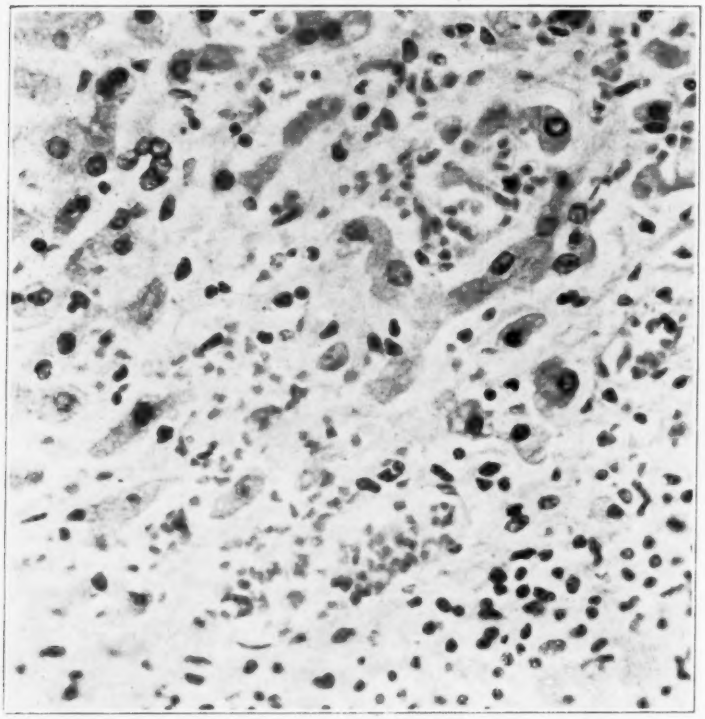

Fig. 6.—Early phase of the lesion showing dilated sinusoids and dissociated, compressed trabeculae.

or vascular spaces (fig. 6). The cords are usually much narrowed and deformed and contain blood pigment. In the unaffected hepatic areas the cells contain no pigment whatever. On the other hand, it is of interest that with stains for glycogen the dissociated liver cells contain none while nearly all the cells of the normal cords stain positively. The much dilated sinusoids are filled with blood and are surrounded by fine fibrils of collagen, and with silver stains, even in the early stages there is a condensation of fibrillar connective tissue within these dilated

sinusoids (fig. 7). At times the sinusoidal spaces are so wide as to be aptly called "blood lakes." One can also note, even at this stage, greater or lesser infiltration with round cells, limited entirely to these areas.

In the later stages the dilated sinusoids become progressively surrounded by fibrillar connective tissue, in which large numbers of round cells are interspersed. The new connective tissue surrounds a vast

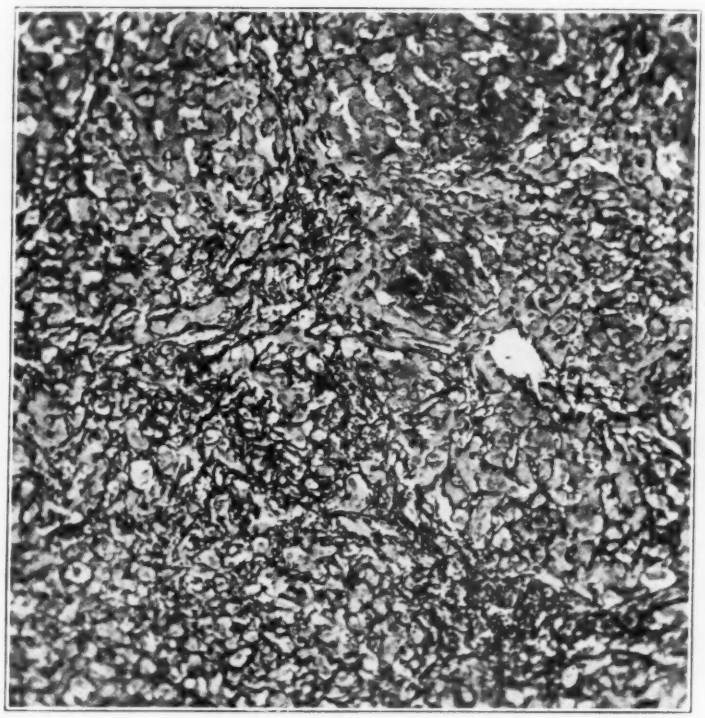

Fig. 7.—Silver stain of a fibrotic area showing condensation of fibrillar connective tissue.

number of vascular spaces varying from those of capillary size to those of the dimensions of an arteriole, resulting in an angiomatous appearance (fig. 8). Within these areas are single cells or multiple cell remnants of liver cords in a greater degree of dissociation; many have even been transformed into newly formed "bile ducts."

If one is lucky enough to find a plane in which these cirrhotic areas can be traced back to their origins in the portal spaces or, better, if one can do this with the aid of serial sections, one notes an arteriole arising

from the portal space and penetrating directly into the cirrhotic area (figs. 9 and 10). In the earlier phases the end of the artery apparently breaks up into the widely dilated sinusoids or blood spaces. So uniformly is this observed that I deem it a distinctive morphologic characteristic of the cirrhosis accompanying diffuse toxic goiter, which suggests (as I shall later discuss) an explanation for the pathogenesis of the lesion. In the late stages the sclerosis is so dense as to obliterate

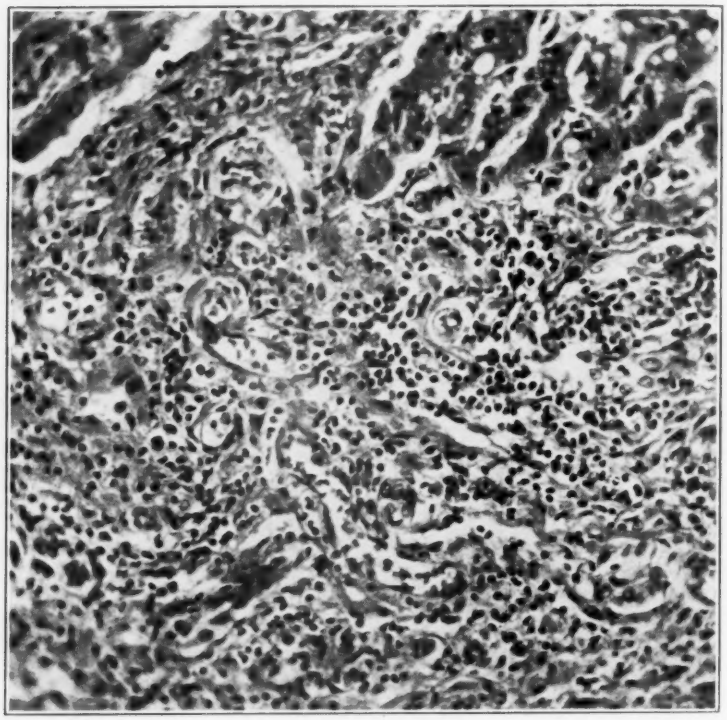

Fig. 8.—Late phase of the lesion showing round cell infiltration, fibrosis and angiomatous appearance.

the finer landmarks, and the relation of these patches to the artery is not so obvious.

The portal spaces aside from their relation to the cirrhotic areas vary morphologically. In most instances they show sparse to moderate round cell infiltration. Such infiltration is common, however, not only in noncirrhotic livers of patients with diffuse toxic goiter but also in livers of persons dying of other maladies. The round cell infiltration has therefore little significance. In many of the livers there was a

moderate increase of the connective tissue in the portal spaces. This was present both in the livers with and in those without cirrhosis. The increase was never sufficient to warrant the diagnosis of insular cirrhosis, and in a parallel series of livers removed from patients dying of other disorders the incidence and the amount of new connective tissue were practically the same.

The portal vein, the hepatic artery and the bile ducts appear normal. The capillaries within the portal spaces show no congestion. The capil-

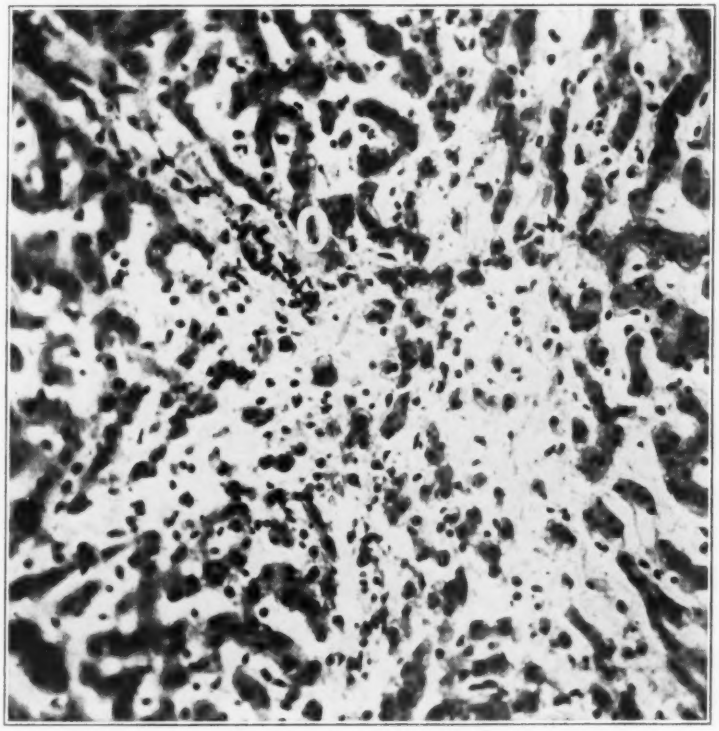

Fig. 9.—Arteriole (*O*) in a vascular septum penetrating into a fibrotic area with dilated sinusoids.

laries arising from the portal vein which penetrate into the interlobular vascular septums occasionally show some dilatation but otherwise reveal no abnormality.

The most common alteration of the parenchymal hepatic cells is a fatty infiltration varying from a slight to a fairly extensive process. It was present in 14 cases. Usually the fatty change is not particularly evident. In a control series of livers removed from patients with other

diseases this infiltration appears somewhat less common, and its intensity is of a lower grade. However, the range of fatty infiltration varies so widely that the distinguishing of the normal from the abnormal is difficult. In my series the fatty change was not more common in livers with than in those without cirrhosis, so that it is not significant in the genesis of the cirrhosis. In a few instances moderate parenchymatous degeneration was noted.

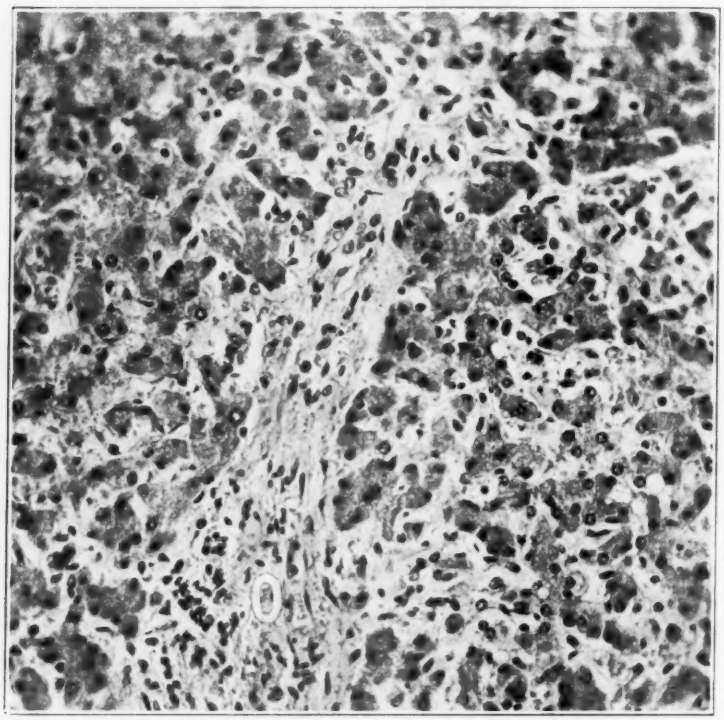

Fig. 10.—Arteriole (*O*) in a vascular septum in a fibrotic area.

Blood pigment, as I have already mentioned, was noted in the parenchymal cells lying within the cirrhotic areas, as well as around the central veins in the livers with associated chronic venous congestion. Although there was a patient who presented clinical jaundice terminally, no bile pigment was observed in the liver cells. In the liver of another patient there were a few small foci of necrosis, characterized by isolated groups of shadow cells that stained but faintly, in which there was a sprinkling of polymorphonuclear cells. This finding was associated with

cirrhosis, but the cirrhotic areas presented no topographic relation to these foci of necrosis.

The characteristic morphologic evidence of chronic venous congestion was found in 13 of 31 cases. In 3 the lesion was associated with cirrhosis. In the remaining 8 cases with cirrhosis there was no chronic venous congestion; in 10 cases chronic venous congestion was unassociated with any other lesion.

The capsule of the liver was normal except in the instances in which subcapsular cirrhosis was present; in these instances it showed slight to moderate thickening and sparse round cell infiltration. In 2 instances a tiny bile duct adenoma was found situated just beneath the capsule. In 1 case a small subcapsular angioma was present. The occurrence of these neoplasms is probably incidental.

"Serous hepatitis" like that described by Rössle [10] was noted in 12 of the 31 cases, an incidence of 38.7 per cent, which is approximately that found by Keschner and Klemperer [18] (43 per cent) in a series of livers of patients dying of diffuse toxic goiter. They also found "serous hepatitis" in 15 per cent of all patients dying from other causes. In my series this lesion was slightly more common in the patients with cirrhosis than in those without, in the proportion of 7 to 5. These facts alone would preclude "serous hepatitis" as the primary event in the causation of this type of cirrhosis. A lesion such as I have described, which is so characteristic of this disorder, cannot reasonably be the result of "serous hepatitis," which is so commonly found in other conditions. I have thus far not found this type of cirrhosis, whether viewed morphologically or topographically, in any other disease. The "serous hepatitis" must therefore be viewed as a secondary manifestation, a point of view also taken by Habán [5] and Zeldenrust and van Beek.[8]

PATHOGENESIS

A clue is offered by the microscopic appearance of the earliest phase of the lesion and its progression. One finds a dilatation of capillaries so marked at times as to lead to focal hemorrhage, with compression and dissociation of the surrounding hepatic trabeculae, the cells of which almost invariably contain blood pigment. In the later phases there is a progressive increase of connective tissue around these dilated spaces, with abundant round cell proliferation and progressive development of the previously dilated capillaries to small venules, affording an angiomatous appearance of the new tissue. The further senescence is characterized by an increase in the amount and the density of the new connective tissue. In appearance and progression the lesion is identical

18. Keschner, H. W., and Klemperer, P.: Frequency and Significance of Hepatic Edema, Arch. Path. **22**:583 (Nov.) 1936.

with that noted in chronic congestion of the liver and its later phase, cardiac cirrhosis. As I have tried to show,[19] cardiac cirrhosis which arises in the presence of hypertension of the pulmonary circulation is due to venocapillary sclerosis consequent to the increased back pressure transmitted downward through the inferior vena cava into the hepatic veins, thence into the central veins and finally into the radiating sinusoids of the lobule. Cardiac cirrhosis is usually associated with sclerosis of the pulmonary artery and of the alveolar capillaries and with sclerosis of the hepatic veins.[20] The earlier lesion is the chronic congestive or nutmeg liver. The capillary sclerosis occurring in the hepatic lobule resembles closely that seen in certain organs of the greater circulation, especially notable in the glomeruli in hypertensive disease, and I have employed the term "arteriocapillary sclerosis" to the summation of this process. However, the cirrhosis which I have described differs in one fundamental aspect from the conventional cardiac cirrhosis, namely that topographically the lesion is never present around the central veins but is found in the interlobular spaces. Although the typical lesion of hepatic venous congestion was present in 3 of the 11 cases, it cannot be regarded as the origin, because venous congestion was completely absent in the remaining 8 cases. The venous congestion was unquestionably the consequence of the superimposed myocardial failure which these 3 patients revealed in their clinical story. Nevertheless, one could not escape the concept that if the origin of the cirrhosis was not primarily cardiac it must at least be circulatory, and it remained to determine what disturbing element in the circulatory dynamics of diffuse toxic goiter might account for the lesion. Inasmuch as the form of the cirrhosis which I have described is apparently pathognomonic of diffuse toxic goiter, it seemed reasonable to assume that some factor in the circulatory dynamics that is peculiar to this disease was responsible. This factor I believe is the increased velocity of the blood flow as measured by the circulation time. Anemia excepted, no other malady is associated with a consistently increased velocity of blood flow.

The increased velocity of blood flow in patients with diffuse toxic goiter was first demonstrated with the radium method by Blumgart, Gargill and Gilligan.[21] Normally they found that the arm to heart

19. Moschcowitz, E.: Pathogenesis of Brown Induration of the Lung, Am. Heart J. **6**:171, 1930.

20. Moschcowitz, E.: Phlebosclerosis of the Hepatic Veins, in Contributions to the Medical Sciences in Honor of Dr. Emanuel Libman, New York, International Press, 1932, vol. 2, p. 857.

21. Blumgart, H. L.; Gargill, S. L., and Gilligan, D. R.: Studies on the Velocity of Blood Flow: The Circulatory Responses to Thyrotoxicosis, J. Clin. Investigation **9**:69, 1930.

circulation time averaged 6.6 seconds, while the crude pulmonary circulation time (from the heart to the arteries about the elbow) averaged 10.8 seconds. In patients with diffuse toxic goiter the arm to heart circulation time averaged 4.9 seconds, while the crude circulation time averaged 5.9 seconds. These findings were confirmed by Tarr, Oppenheimer and Sager,[22] employing the sodium dehydrocholate method, and by many others since. The finding of a rapid circulation time confirms a surmise afforded by clinical observation that in exophthalmic goiter the skin is flushed and warmer than normal, that there is a feeling of increased heat although the rectal temperature is within the normal range, that there is increased perspiration and that the pulse pressure is increased. All observers agree that in mass data there is a correlation between the velocity of the blood flow and the basal metabolic rate, although in an individual case this relation does not always hold. Moreover, the increased velocity of blood flow in patients with diffuse toxic goiter is inseparably linked with an increased blood volume,[23] an increased cardiac output [24] and an increased peripheral blood flow as measured by the formula cc./sq.M./min.[25] These factors in the circulatory dynamics of the disease are reversible after the administration of strong solution of iodine U. S. P. and especially after subtotal thyroidectomy. In myxedema the opposite relations are maintained.[25]

The significance and the interrelationships of these disturbed circulatory functions and the compensatory adjustments have by no means been clarified. Such a discussion is reserved for a future communication on a planned study of the cardiodynamics of patients with diffuse toxic goiter. For the present, I am concerned only with their factual presence and their bearing on the pathogenesis of the cirrhosis which I have described. To elucidate my concept a knowledge of the circulation of the liver is essential.

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22. Tarr, L.; Oppenheimer, B. S., and Sager, R. V.: The Circulation Time in Various Clinical Conditions Determined by the Use of Sodium Dehydrocholate, Am. Heart J. **8**:766, 1933.

23. (*a*) Liljestrand, G., and Stenström, N.: Blood Flow and Blood Pressure in Exophthalmic Goitre, Acta med. Scandinav. **63**:99, 1925. (*b*) Chang, H.: The Blood Volume in Hyperthyroidism, J. Clin. Investigation **10**:475, 1931. (*c*) Stewart, H. J., and Evans, W. F.: The Peripheral Blood Flow in Ten Women Exhibiting Graves' Disease, J. Mt. Sinai Hosp. **8**:1051, 1942. (*d*) Gibson, J. G., Jr., and Harris, A. W.: Clinical Studies of the Blood Volume: Hyperthyroidism and Myxedema, J. Clin. Investigation **18**:59, 1939.

24. Fullerton, C. W., and Harrop, G. A., Jr.: The Cardiac Output in Hyperthyroidism, Bull. Johns Hopkins Hosp. **46**:203, 1930. Boothby, W. M., and Rynearson, E. H.: Increase in Circulation Rate Produced by Exophthalmic Goitre, Arch. Int. Med. **55**:547 (April) 1935. Liljestrand and Stenström (*23a*).

25. Evans, W. F., and Stewart, H. J.: Peripheral Blood Flow in Myxedema, Arch. Int. Med. **69**:808 (May) 1942.

The Vascular Supply of the Liver.—Aside from the lung, the liver is the only organ that has both an arterial and a venous supply, but whereas the bronchial artery carries only a small fraction of the total blood to the lungs and supplies only the supporting tissues of that organ, the hepatic artery carries a much greater quantity of blood, estimated by Burton-Optiz [26] as approximately 25 per cent, by Barcroft and Shore [27] as 39 per cent, by MacLeod and Pearce [28] as 26 to 32 per cent and by Grab, Janssen and Rein [29] as between 12 and 22 per cent. Furthermore, the hepatic artery supplies not only the supporting structures but also, though to a lesser degree than the portal vein, the parenchyma. This is clearly manifest in an animal with an Eck fistula, in which the liver remains viable and even retains many of its functions, although to a lesser degree than is normal, for an appreciable period.[30] In this connection the observation of Barcroft and Shore [27] is pertinent. They found that the liver, in both fasting and fed animals, takes its dominating supply of oxygen from the hepatic artery. The hepatic artery is therefore of much greater physiologic significance than the bronchial.

While most observers are agreed on the manner of distribution of the portal blood supply of the hepatic lobule, controversy still centers on the precise mode of communication between the portal vein and the hepatic artery within the liver, and it is in the elucidation of this anatomic arrangement that, I believe, the pathogenesis of the cirrhosis occurring in the livers of patients with diffuse toxic goiter depends. That the portal vein and the hepatic artery communicate within the liver has been amply demonstrated not only by the Eck fistula but more directly by the observation that blood injected into the hepatic artery escapes from the portal vein and, but to a lesser degree, vice versa. Now, inasmuch as the pressure within the hepatic artery is practically that within the brachial, i. e., 130 mm. of mercury,[31] and the pressure in the portal vein is low, estimated to be between 6 and 12 mm. of mercury,[31] these pressures must be neutralized somewhere within the liver. The earlier authors accepted the theory of Gad,[32] who postulated that the union

26. Burton-Opitz, I. R.: The Vascularity of the Liver: I. The Flow of Blood in the Hepatic Artery, Quart. J. Exper. Physiol. **3**:297, 1910.

27. Barcroft, J., and Shore, L. E.: The Gaseous Metabolism of the Liver: I. In Fasting and Late Digestion, J. Physiol. **45**:296, 1912-1913.

28. MacLeod, J. J. R., and Pearce, R. G.: The Outflow of Blood from the Liver as Affected by Variations in the Condition of the Portal Vein and Hepatic Artery, Am. J. Physiol. **25**:87, 1914.

29. Grab, W.; Janssen, S., and Rein, H.: Ueber die Grösse der Leberdurchblutung, Ztschr. f. Biol. **89**:324, 1929.

30. Whipple, G. H., and Hooper, C. W.: Bile Pigment Output Influenced by the Eck Fistula, Am. J. Physiol. **42**:544, 1917.

31. MacLeod, J. J. R.: MacLeod's Physiology in Modern Medicine, ed 9, St. Louis, C. V. Mosby Company, 1941, p. 503.

between the arterial capillaries and the portal channels occurs at an acute angle, forming at these points a wedge-shaped valve which shifts as the pressure bears on the sides of the flap. With normal pressure the valve permits an even flow from the arterial to the venous channels. When pressure is increased in the portal vein, flow and pressure are reduced in the hepatic artery, and vice versa. All later observers have abandoned this hypothesis because it ignored the capillary network that has since been amply demonstrated between the two vessels.

While the distribution of the blood from the portal vein to the sinusoids of the liver has been well clarified, the demonstration of the terminal ramifications of the hepatic artery has been the subject of much dispute. It has long been accepted since the pioneer work of Kiernan,[33] and repeatedly confirmed, that the hepatic artery terminates, within the capsule of Glisson, in capillaries of slender caliber which supply the walls of the bile ducts, the larger branches of the portal vein (vasa vasorum) and the connective tissue structure of the capsule itself. For a long time this was regarded as the sole function of the hepatic artery, and even in comparatively modern times some observers still hold to this view. Inasmuch as it was known that the portal vein and the hepatic artery communicate, it was assumed that these capillaries eventually formed venules, the internal hepatic venules or rami vasculosi venosi, which then supplied the hepatic sinusoids, thus establishing a communication between the artery and the vein. More recent observations of Mall,[34] Olds and Stafford,[35] Fiessinger and Walter[36] and Aunap[37] have shown that these venules do not exist. Observers are agreed that there is no communication between the capillaries of the hepatic artery and the portal vein within the capsule of Glisson proper. The communication must therefore occur outside the capsule.

Experiments in which a visualizing material was injected directly into the hepatic artery have shown that this vessel terminates in a capillary network that supplies the walls of the bile ducts and the portal vein within the capsule of Glisson. But the periphery of the hepatic lobule is also filled. This is accomplished in large part by a narrow

32. Gad, J.: Studien über Beziehungen des Blutstroms in der Pfortader zum Blutstrom in der Leberarterie, Inaug. Dissert., Berlin, G. Schade, 1873.

33. Kiernan, F.: The Anatomy and Physiology of the Liver, Phil. Tr., London **123**:711, 1833.

34. Mall, F. P.: A Study of the Structural Unit of the Liver, Am. J. Anat. **5**:227, 1906.

35. Olds, J. M., and Stafford, E. S.: On the Manner of Anastomosis of the Hepatic and Portal Circulations, Bull. Johns Hopkins Hosp. **47**:176, 1930.

36. Fiessinger, N., and Walter, H.: L'exploration functionelle du foie et l'insuffisance hépatique, Paris, Masson & Cie, 1925.

37. Aunap, E.: Ueber der Verlauf der Arteria hepatica in der Leber, Ztschr. f. mikr.-anat. Forsch. **25**:238, 1931.

arteriole [38] that courses in the vascular septums, whence it breaks into capillaries that supply the adjacent sinusoids. To a much lesser degree some of the capillaries that supply the large bile ducts communicate directly with the peripheral sinusoids of the hepatic lobule. These

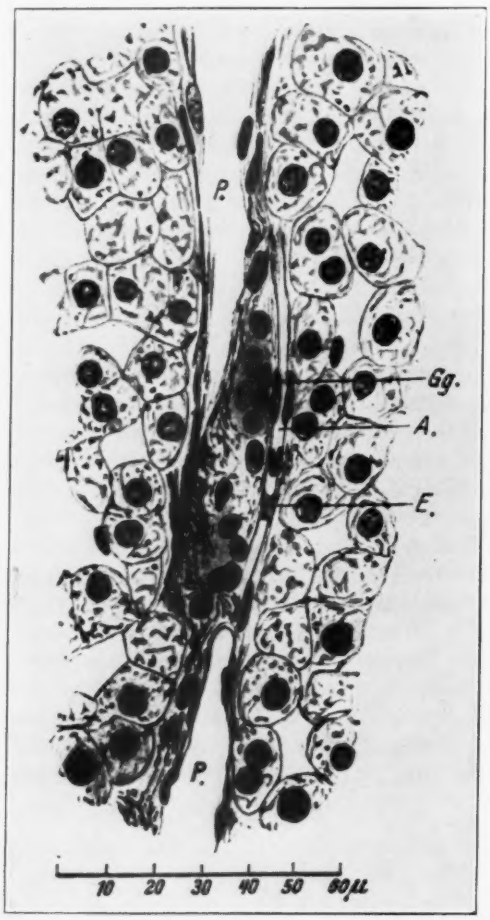

Fig. 11.—High power illustration of a normal vascular septum: *P.*, portal venule; *A.*, arteriole; *Gg.*, bile duct; *E.*, a longitudinally compressel erythrocyte. (The illustration is taken from Pfuhl.[17])

38. Gilbert, A., and Villaret, M.: Contribution à l'étude de la circulation du lobule hépatique, Compt. rend. Soc. de biol. **67**:521, 1909. Geraudel, E.: La double circulation capillaire de la glande hépatique, ibid. **58**:818, 1905. Mall.[34]

arterioles are always accompanied by a small branching portal venule and by a tiny bile duct (fig. 11). These three structures penetrate between the individual lobules, and the vascular channels break up and communicate between the nodal points by a fine capillary network that surrounds each lobule (fig. 12). In the pig these interlobular structures are particularly prominent. These vessels have been termed vasa interlobularia by Kiernan [33] and rami vasculares septales by Pfuhl.[17] Olds and Stafford [35] have shown by serial sections that these arterioles represent the so-called translobular arteries described by Braus.[39] Acording to Pfuhl,[17] these arterioles are very slender, averaging 8 microns in diameter, and consist of an endothelial lining and

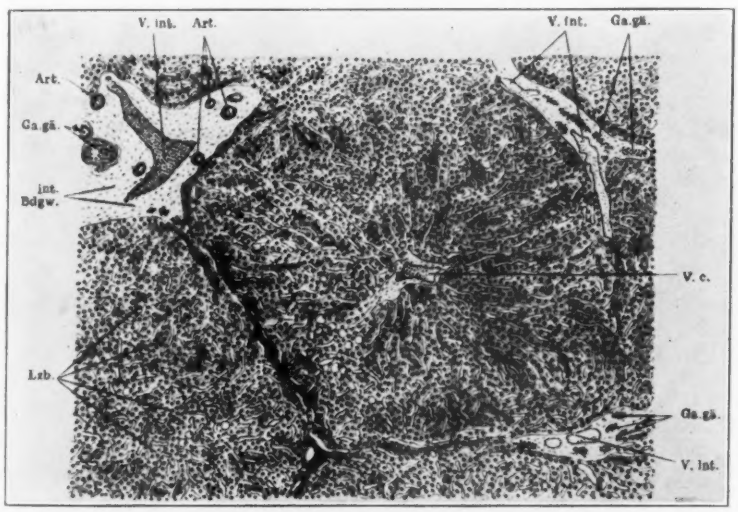

Fig. 12.—Diagrammatic representation of a normal hepatic lobule: *Art.*, arterial branches; *Ga. gä.*, bile ducts; *int.* interlobular connective tissue; *Lzb.*, hepatic trabeculae *V.c.*, central vein; *V. int.*, interlobular vein. (The illustration is taken from Sobotka, J.: Textbook of Human Histology and Microscopic Anatomy, New York, G. E. Stechert & Company, 1930, vol. 2.)

a sparse adventitia containing cells which, he believes, possess contractile powers (fig. 13). However, in studying many sections of normal livers I have noted that occasionally the walls contain muscle bundles, both longitudinal and transverse. It is noteworthy, for the interpretation of the peculiar localization of the cirrhosis of diffuse toxic goiter, that these interlobular arterioles arise only in the smaller division of the capsule of Glisson—according to Mall, "throughout the extent of the

39. Braus, H.: Anatomie des Menschen, Berlin, Julius Springer, 1924.

vessels of the sixth and possibly of the fifth order" (fig. 14). Quoting Olds and Stafford,[35]

. . . the hepatic arterial capillaries do not anastomose directly with the portal vein radicles within the portal spaces. Instead, the arterial capillaries enter the hepatic sinusoids independently of the venous anastomoses. Slender capillaries arise either as the ultimate radicles of fine branches of the hepatic artery, or as

Fig. 13.—Vascular septum of normal human liver; *G.*, septal bile duct; *A.*, artery; *P.*, branch of portal vein. (This illustration is taken from Pfuhl.[17])

offshoots from the capillary plexuses surrounding the bile ducts. These capillary branches course towards the periphery of the portal space and anastomose with the hepatic sinusoids. The junctions of the arterial capillaries with the sinusoids are always independent of, and at some distance from, the similar communications established by the veins. Hence the most peripheral sinusoids are initially either distinctly arterial or venous, as the case may be. The venous connections are more

numerous, approximately four to five venules communicating with the sinusoids of a lobule to one arterial connection.

The portal venous capillary network is therefore correspondingly more extensive than the hepatic arterial network and contributes the first and a significant factor in equalizing the difference in pressures between the hepatic artery and the portal vein within the hepatic parenchyma by lowering the peripheral resistance. There is a second anatomic factor that helps in the equalization of pressures. Mall,[34] Aunap [37] and Olds and Stafford [38] have shown that the average diameter of the terminal hepatic arterioles is only 8 microns, whereas the average diameter of the hepatic sinusoids is 9 microns, so that at the point of

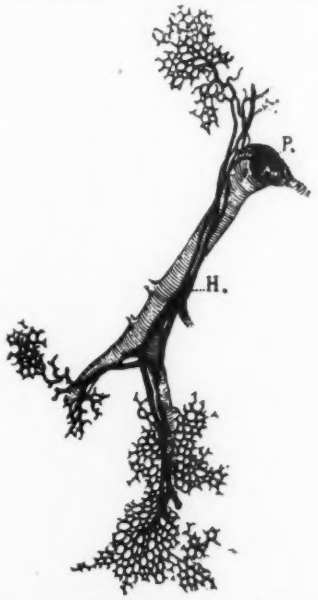

Fig. 14.—Diagrammatic representation of the smallest divisions of a portal space, showing the termination of the hepatic artery: *P.*, portal vein; *H.*, hepatic artery. The portal vein was first plugged with a granular mass and then an aqueous solution of prussian blue was injected into the artery. The extent of the capillary injection of the blue is shown. (This illustration is taken from Mall.[34])

communication with the sinusoids there is a sudden abrupt widening (fig. 15). This observation was confirmed by Wakim and Mann [40] when they directly observed blood flow in living amphibian and mammalian livers by the technic of quartz-rod illumination. Although this difference in caliber appears small, the effect on the blood flow is con-

40. Wakim, K. G., and Mann, F. C.: The Intrahepatic Circulation of the Blood, Anat. Rec. **82**:233, 1942.

siderable when the difference in diameter is multiplied by the large number of such arterioles within the organ. A third factor in the equalization of pressures arises from anastomotic communications between the corresponding ramifications of the portal vein and the hepatic artery in their interlobular course. These have been demonstrated by Wakim and Mann in both amphibian and mammalian livers,

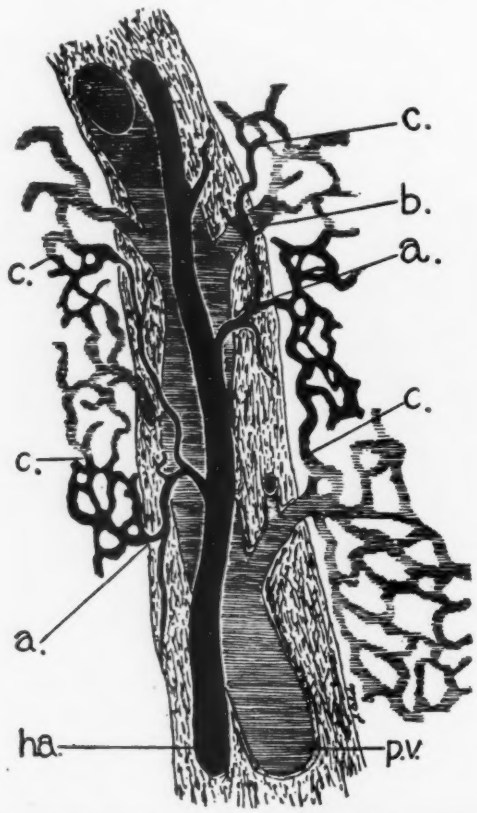

Fig. 15.—A longitudinal section through an interlobular or portal space. Note the distribution of the hepatic arterioles (*a.*), portal venules (*b.*) and the intersinusoidal communications (*c.*). The abrupt transition from narrow arterial channel to wide sinusoidal channel is illustrated. Note the mixing of the two injection masses at the level of the first sinusoidal anastomosis and thereafter. (This illustration is taken from Olds and Stafford.[35])

though not so frequently in the latter as in the former (fig. 16). These observers also noted that arterial ramifications end in the terminal branches of the portal vein before the latter empty into the sinusoids at the peripheries of the lobules.

Synthesis.—The equalization of pressure between the hepatic artery and the portal vein within the liver is accomplished in greater part at least by an intercommunicating capillary network whereby blood flows from a small basin to one four or five times as great, from a conducting system of narrow vascular channels to those of slightly larger diameter, and finally by arteriovenous communications interposed between the terminal ramifications of the two vessels. The peripheries of the hepatic lobules are therefore supplied by either arterial or venous blood and

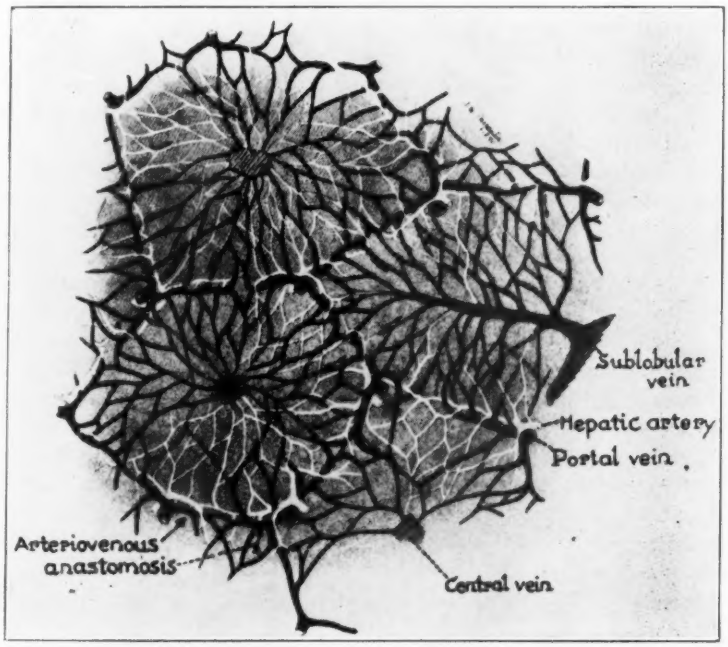

Fig. 16.—Diagrammatic representation of the communication of the arterial and the venous blood within the mammalian liver. White identifies the arterial, black the portal and shading the hepatic venous radicles. Anastomoses between the arterial and the portal radicles as they course through the interlobular spaces are noted here. (The illustration is taken from Wakim and Mann.[40])

only to a much lesser extent by an admixture of both bloods. It is only in the deeper sinusoids of the liver that all the arterial and the venous blood eventually meet (fig. 17).

My description refers entirely to static conditions. The vascular supply of the liver is profoundly influenced by vasomotor reactions, and this affects the function of the liver in providing a blood depot, in regulating the supply of blood to the right side of the heart and in inte-

grating these vasomotor responses with those in other systemic vessels.[41] How these reactions are affected in patients with diffuse toxic goiter is not known.

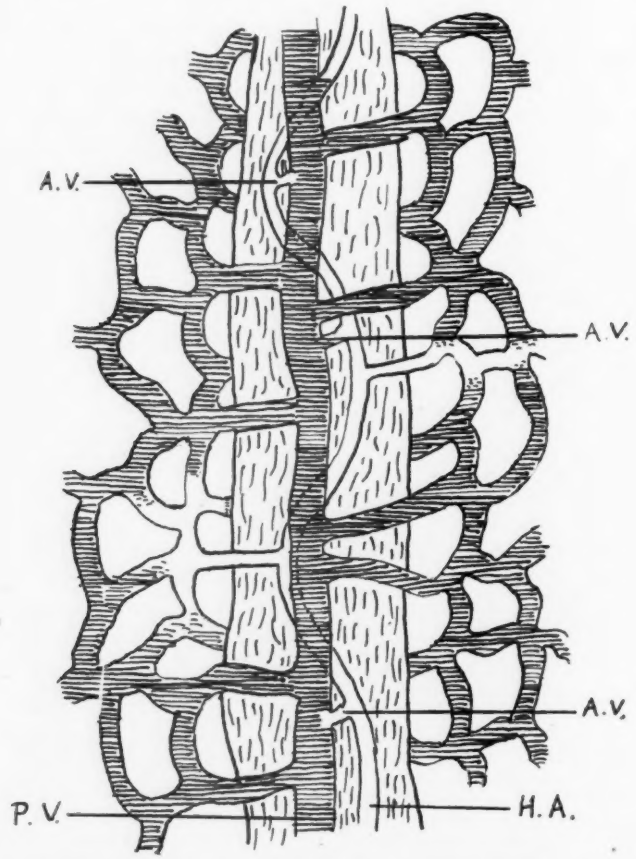

Fig. 17.—Diagrammatic representation of a vascular septum showing the different mechanisms whereby the intravascular pressures are equalized between the hepatic artery and the portal vein. Note (1) the communications between the terminal capillaries of the hepatic artery and the terminal capillaries of the portal vein in the border zones of the adjacent lobules and the sudden widening of arterial capillaries into venous; (2) the larger number of the portal branches as compared with the arterial; (3) the arteriovenous anastomoses within the vascular septum. The bile duct has been omitted, for purposes of clarification. (The illustration is a modification from Olds and Stafford.[35]) *H.A.* indicates the hepatic artery *P.V.* the portal vein; *A.V.* the arteriovenous anastomoses.

41. Katz, L. N., and Rodbard, S.: The Integration of the Vasomotor Responses in the Liver with Those in Other Systemic Vessels, J. Pharmacol. & Exper. Therap. **67**:407, 1939.

These anatomic considerations in association with the altered circulatory dynamics in patients with diffuse toxic goiter lead to the following interpretation of the pathogenesis of this peculiar type of hepatic cirrhosis.

It should be recalled that, as best determined in the early phases of the lesion, the areas of cirrhosis are wedge shaped and, when confluent, stellate, and are situated between the lobules; also, that in serial sections the narrow portion of the wedge can be traced to the splitting up of a branch of the hepatic artery that arises from the Glisson capsule and penetrates in the vascular septums, when it proceeds directly either through the peripheral portions of two adjacent lobules or through an entire lobule and terminates in a central vein or in a collecting vein arising from the conglomeration of a number of central veins. It is therefore at the site where the interlobular hepatic artery supplies the periphery of the hepatic lobule—the predominant location of intrahepatic equalization of the pressures between the hepatic artery and the portal vein—that the cirrhotic process arises. This observation is consistent with the fact that such cirrhotic areas are visible only in the neighborhood of the smaller divisions of the capsules of Glisson, from which these narrow hepatic arterioles exclusively arise. Furthermore, it should be recalled that with higher magnifications the early manifestations of the cirrhotic process are represented by pronounced capillary dilatations, with corresponding trabecular atrophy, which eventually parallel the finer morphologic characteristics of a congestive liver. To account for this I now invoke the clinical observation, particularly peculiar to diffuse toxic goiter, that there is increased velocity of blood flow and that this is associated with increased blood volume and increased arterial blood flow. While compensatory adjustments to the increased velocity of blood flow undoubtedly occur in the early phases of this disease, eventually this disturbance of circulatory dynamics must take its toll, so that the blood which enters the terminal ramifications of the hepatic artery no longer can be carried away as fast as it enters. The intrahepatic equalization of pressure between the hepatic artery and the portal vein is no longer maintained; stasis must ensue, resulting in dilatation of the neighboring capillaries. In time this is projected deeper into the parenchyma until the dilated capillaries pour their blood into the central or the collecting veins. The time factor is obviously of importance, which explains why the cirrhosis is observed usually in the later phases of the disease. In this respect it is precisely comparable to cardiac cirrhosis. In other words, the morphologic beginnings and subsequent progression of this lesion are precisely what I have tried to demonstrate as capillary sclerosis in cardiac cirrhosis arising in congestive failure,[23d] the difference being that in cardiac cirrhosis there is backward failure, while in the cirrhosis of diffuse toxic goiter the failure

occurs in a forward direction. Topographically the lesions of the two types of cirrhosis are different; in cardiac cirrhosis the lesion begins around the central vein; in the cirrhosis of diffuse toxic goiter, it is at the periphery of the lobule. In diffuse toxic goiter, if chronic congestion is superimposed, both sites are involved. Parenthetically, the increased velocity of blood influences the circulatory dynamics in other respects. This is suggested by the clinical observation that in about a third of patients with diffuse toxic goiter the pulmonary conus is enlarged.[42] Curiously, Saltykow[43] reported a peculiar type of congested liver that differed from the conventional nutmeg type in that the congestion was not around the central vein but was between the branches of the periportal connective tissue, in the form of projections which eventually became star shaped and might even encircle a lobule or lobules. This description resembles closely that of the cirrhosis of diffuse toxic goiter. Regrettably Saltykow gives no clinical correlations.

My interpretation of the pathogenesis necessitates an explanation of the noteworthy subcapsular predilection of the lesion. This predilection is not peculiar to this form of cirrhosis, and it is interesting that it is usual in the livers of patients with congestive failure.[44] Inasmuch as there is not the slightest evidence that there is a difference of vascularity in these areas, local conditions must be ascribed as the cause. I feel strongly that the peripheral resistance engendered by the firm capsule of the liver is the main if not the only factor. This was suggested by Fahr[44b] as the cause of the subcapsular prominence of the lesions of the congested liver, and there are a number of reasons for assuming similar mechanisms for the cirrhosis of diffuse toxic goiter. First, as was shown in a previous study,[45] one of the important factors in the localization of arteriosclerosis and phlebosclerosis is the degree of external resistance surrounding the involved vessel—for instance, the prominence of patches of sclerosis of the aorta at the site of the intervertebral disks as compared with the hollows between[46]; the greater incidence of patches of sclerosis of the pulmonary artery where the vessels lie against the firm rings of the bronchi[45]; the predilection of

42. Parkinson, J., and Cookson, H.: The Size and Shape of the Heart in Goitre, Quart. J. Med. **24**:499, 1931.

43. Saltykow, S.: Ueber Stauungsleber, Verhandl. d. deutsch. path. Gesellsch. **5**:104, 1902.

44. (*a*) Gerlach, W., in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1930, vol. 5, p. 90. (*b*) Fahr, T.: Zur Frage der chronischen Stauungsleber, Zentralbl. f. Herzkrankh. **4**:368, 1912.

45. Moschcowitz, E.: Vascular Sclerosis, New York, Oxford University Press, 1942.

46. Westenhoeffer: Ueber die Lokalisation und phylogenetische Grundlage der Aorta und ihrer Aeste, Deutsche med. Wchnschr. **48**:518, 1922.

patches of sclerosis for those areas of arteries that lie against bone (this is seen in the arteries of the calvarium [47] and in the radial artery [48]); finally, the Cramer and Schilling [49] area of sclerosis in the lower end of the inferior vena cava which lies against the rigid aorta and where the two currents of the common iliac veins meet. Now, the incidence of capillary sclerosis parallels that of vascular sclerosis; this is exemplified in the glomeruli and the islands of Langerhans in hypertension of the greater circulation, in the walls of the pulmonary alveoli in hypertension of the pulmonary circuit and around the hepatic central veins in sclerosis of the hepatic vein in long-standing congestive failure,[45] so that sclerosis of the larger vessels and capillary sclerosis are usually simultaneous lesions. That external resistance is a factor in the production of capillary sclerosis is additionally exemplified by my observation that the most prominent lesions are witnessed in the peripheral portions of the lung where the capillaries are adjacent to the pleural surface and that sclerosis of the hepatic parenchyma occurs immediately adjacent to a greatly dilated hepatic vein (fig. 18).

Finally, the factor of external capsular resistance is well exemplified in a liver from a person who died of cardiac failure in the course of diffuse toxic goiter. On the surface of the liver were two deep grooves, the result of pressure from two abnormally situated ribs. Although the organ did not reveal the characteristic cirrhosis of diffuse toxic goiter, but only evidences of marked chronic congestion, there was in the subcapsular areas a considerable increase of connective tissue, which extended a short distance into the parenchyma and was limited exclusively to the grooves (fig. 19). The lesion resembled that found in the late phases of cardiac cirrhosis.

One may well inquire why the cirrhosis of diffuse toxic goiter is sometimes absent in cases in which the history of the disease is apparently one of long duration. In 3 of my cases without cirrhosis the duration of the disease was given as one year or more. It is interesting to note that in all 3 chronic venous congestion was shown at autopsy; in 2 there was associated disease of the coronary arteries. It is probable that the circulatory dynamics were modified by the incidence of venous congestion. Blumgart, Gargill and Gilligan [21] and Tarr, Oppenheimer and Sager [22] have shown that the onset of congestive failure prolongs the circulation time to normal limits. According to Tarr and

47. Lauda, E.: Physiologische Druckschädigungen und Arteriosklerose der Duralgefässe, Beitr. z path. Anat. u. z. allg. Path. **58**:180, 1921.

48. Dow, D. R.: The Incidence of Arteriosclerosis in the Vessels of the Body, Brit. M. J. **2**:162, 1925.

49. Cramer, H.: Beiträge zur Atherosklerosefrage, Virchows Arch. f. path. Anat. **230**:46, 1921. Schilling, W.: Ueber Phlebosklerose, ihre Enstehungsweise und Ursachen, ibid. **262**:658, 1926.

co-workers, the circulation time in patients with congestive failure and diffuse toxic goiter seems to be an arithmetical average of what would be expected in either condition alone. It is certain that congestive failure may arise in patients with diffuse toxic goiter before cirrhosis occurs; this is proved by the finding of a congested liver without cirrhosis in 10 of my series. In 2 of the 3 cases of long duration the congestive failure was probably induced by an associated disease of the coronary vessels.

Fig. 18.—Area of marked fibrosis surrounding a greatly dilated large branch of a sclerotic hepatic vein (*O*) of a patient with marked congestive failure.

HEPATIC CHANGES IN EXPERIMENTAL HYPERTHYROIDISM

It was natural to infer that this type of cirrhosis might be reproduced experimentally by administration of thyroid. Attempts to do this have been fully summarized by Lichtman.[50] The findings aside from depletion of glycogen have been inconsistent. Some observers have reported fatty or parenchymatous degeneration; others have reported increases

50. Lichtman, S. S.: Diseases of the Liver, Philadelphia, Lea & Febiger, 1942, p. 621.

of weight despite the depletion of glycogen. Some have reported foci of necrosis after thyroid feeding; others have not. When foci of necrosis were found, there was always an associated infection, so that it is impossible to say whether the necrosis was caused by the thyroid feeding or by the infection or by a combination of both. No one has even remotely reproduced the type of cirrhosis I have discussed, and this might have been expected for the reason that genuine diffuse toxic goiter has not been successfully reproduced experimentally. At most only part of the

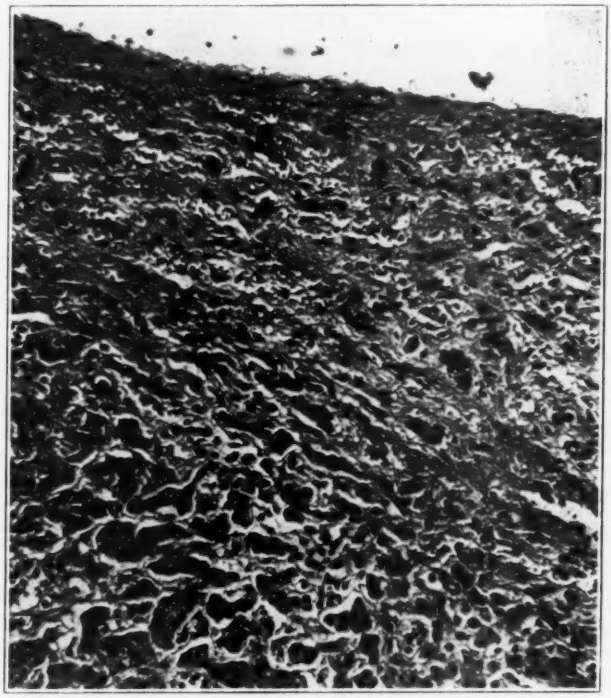

Fig. 19.—An area of marked fibrosis limited exclusively to the subcapsular area and caused by pressure of a rib in a person with congestive failure.

picture has been reproduced, namely, the hyperthyroid element. As I pointed out in a previous communication,[15] exophthalmic goiter represents hyperthyroidism plus a number of other features. This is why I do not regard hyperthyroidism and exophthalmic goiter, or diffuse toxic goiter, as synonymous terms.

SUMMARY

A type of hepatic cirrhosis apparently pathognomonic of diffuse toxic goiter was found in 10 of 31 cases. The lesion is identical in both

form and progression with that seen in chronic hepatic venous congestion and cardiac cirrhosis but differs from the latter in that topographically it is not around the central veins but in the interlobular septums, often encroaching on the lobule itself. In the early phases the areas of fibrosis can be traced to the terminal ramifications of the hepatic artery as it passes into the interlobular vascular septums. This artery and its ramifications represent a significant factor of the equalization of intravascular pressures between the hepatic artery and the portal vein within the liver.

Pathogenetically, I believe, the lesion is the consequence of the increased velocity of blood flow, an invariable accompaniment of, and almost peculiar to, this disease in the early phases. The increased velocity is associated with increased blood volume and increased blood flow. These altered circulatory dynamics render the maintenance of the normal pressure relations between the hepatic artery and the portal vein difficult; eventually decompensation arises, with resulting stasis in these areas, and the lesion begins as capillary congestion. In time, just as in chronic venous congestion of central origin, capillary sclerosis results, with eventual fibrosis. In this conception, the cirrhosis of diffuse toxic goiter is the consequence of forward failure, while that of chronic hepatic venous congestion is the result of backward failure. The cirrhosis is distinguished by the fact that it is predominantly in the subcapsular zone of the liver. Evidence is submitted that, as in the ordinary congestive liver, this is due to the resistance offered by the capsule of the liver. The cirrhosis also possesses the peculiarity that it arises only from the smaller subdivisions of the portal spaces. This is because the interlobular brances of the hepatic artery arise only from such spaces. The cirrhosis bears a definite but not absolute relation to the duration of the malady, which is what one might expect from the pathogenesis. Nevertheless, this cirrhosis is sometimes absent in persons who submit a history of apparent long duration of the disease. This may be accounted for by the observation that chronic venous congestion is an exceedingly common sequence of long-standing diffuse toxic goiter, even in patients without cirrhosis, and that this venous congestion neutralizes the increased velocity of blood flow.

CANICOLA FEVER

Case Report and Review of the Literature

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CANICOLA fever, or leptospirosis canicola, is a rare disease. Although there is an abundance of literature on Weil's disease, or leptospirosis icterohaemorrhagica, there is a paucity of written material on canicola fever. Consequently it was felt advisable to present this case which was seen by the author and to review the literature on the subject.

REPORT OF A CASE

A 44 year old captain of Italian extraction entered Fitzsimons General Hospital on Oct. 1, 1945, giving a history of having suffered a sudden onset of sharp pain across the bridge of his nose with associated nasal congestion during the evening six days previous to admission. Within an hour after the onset of his difficulties the patient had a headache and pains in his hips. He also felt feverish and was sweaty. He took to his bed and remained there for the succeeding four days with little change in symptoms. Since the patient was in San Antonio at the time on an emergency leave that had almost expired, he began driving toward Denver on the fifth day of his illness. During this day the patient noted that his eyes were bloodshot, and on the night of the fifth day he suffered severely from generalized arthralgia, myalgia, anorexia, malaise and nasal congestion. He continued driving on the sixth day of his illness; however, the muscle pains and malaise continued.

Physical examination on admission revealed the patient to be considerably jaundiced and acutely ill. His temperature taken orally was 103 F. His liver was felt 1 fingerbreadth below the right costal margin on deep inspiration and was slightly tender. The spleen was not palpable, and there was no lymphadenopathy. There was marked bilateral conjunctival injection. No costovertebral tenderness was present, nor was there evidence by physical examination of pneumonia or meningitis. Examination otherwise revealed nothing except for evidence of hypertrophic arthritis from which the patient had suffered for a few years.

Laboratory studies at the time of the patient's admission revealed a white blood cell count of 22,900, with 88 per cent polymorphonuclear cells. The red cell count was 4,250,000. The icteric index was 94; the corrected sedimentation rate was 26 mm. per hour; the cephalin-cholesterol reading was 2 plus, and the nonprotein nitrogen was 35 mg. per hundred cubic centimeters. The urine was normal except for the presence of bile, and the stools were light in color.

On admission the patient was started on a low fat, high carbohydrate, high protein diet with supplementary vitamins. He was rather anorexic during his first few hospital days and complained bitterly of generalized pains in joints and muscles and nasal congestion. On the third hospital day a roentgenogram of the

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chest revealed bronchopneumonia at the right cardiophrenic angle. Administration of sulfadiazine was started, but due to lack of therapeutic response it was supplanted by penicillin on the sixth hospital day. This also failed to relieve significantly the patient's symptoms and was discontinued on the twelfth hospital day; however, the pulmonary infiltration had disappeared four days previously. By the tenth hospital day the patient's jaundice was much improved (the icteric index was 29.), although his myalgia and arthralgia persisted and was associated with a daily temperature between 100 and 102 F. orally. The conjunctival injection did not improve and caused the patient a great deal of discomfort. His white blood cell count had fallen to 12,000, with 60 per cent polymorphonuclear cells by this time. Shortly after the tenth hospital day the patient began to make a slow but steady improvement. His fever, arthralgia and myalgia were completely gone by the twenty-fifth hospital day, but his conjunctival injection proved obstinate and continued for his first thirty-five hospital days. The nature of this was unclear. Definite thickening of the bulbar conjunctivas developed, and three small nodules appeared on the right bulbar conjunctiva. All of this eventually cleared.

Agglutinations to Leptospira icterohaemorrhagiae were tried on the thirteenth hospital day with doubtful results. The patient was then questioned as to whether his dog had been ill, and it was learned that the patient's dog had been suffering from a severe, albeit ill defined, illness for the preceding two months. It was also learned that the patient was extremely fond of his dog and was in the habit of fondling the dog a great deal. Consequently the dog was obtained and samples of urine and blood were taken. Samples of serum from both the patient (taken on the twenty-fifth hospital day) and his dog were sent to the National Institute of Health, where it was discovered that both the serums agglutinated Leptospira canicola to a dilution of 1:100,000 and L. icterohaemorrhagiae to 1:1,000. Leptospiras were never seen in the patient's blood by dark field examination; however, they were found repeatedly in the patient's urine between the sixteenth and the twenty-ninth hospital day. Unfortunately the leptospiras were never isolated. No leptospiras were found in the dog's urine, but this may have been due to overvigorous alkalinization.

The patient was sent on a thirty-day convalescent leave on his forty-seventh hospital day. At this time he was asymptomatic. His corrected sedimentation rate was 12 mm. per hour; the cephalin-cholesterol reading was 2 plus, and the icterus index 13. His white blood cell count, serum proteins, alkaline phosphatase, hippuric acid excretion and nonprotein nitrogen were normal. The last four of these were never abnormal during his disease. On his return from his leave all his laboratory studies for evidence of hepatic damage were negative. A mild anemia which developed during his disease had disappeared. He had been asymptomatic during his leave and was discharged from the hospital.

It is of interest that at no time did the patient show evidence of nephritis, meningitis or hemorrhagic tendencies other than the conjunctival injection. Lumbar puncture was not performed.

HISTORY AND INCIDENCE

L. canicola was first isolated by Klarenbeek and Schüffner[1] in 1931. The leptospiras were differentiated from L. icterohaemorrhagiae

1. Klarenbeek, A., and Schüffner, W.: Appearance in Holland of Leptospira Differing from Weil Strain, Nederl. tijdschr. v. geneesk. **77**:4271-4272 (Sept. 16) 1933.

by serologic methods. Although Schüffner [2] mentioned that a case of human infection with L. canicola was seen by a Dr. Cleyndert, of Delft, in September 1933, the first cases of this disease in human beings to be fully reported were those of Roos, Walch-Sorgdrager and Schüffner [3] in 1937. They reported 11 cases from Holland, which is still the largest group of cases assembled by a single group of observers. The first case of the disease in a human being in the United States was reported in 1938 by Meyer, Eddie and Stewart-Anderson [4] from San Francisco. As far as I have discovered this is the thirty-first case to be reported from the entire world and the sixth case from the United States. Cases have been reported from Holland,[5] Austria,[6] Denmark [7] and China,[8] and from San Francisco,[9] New Orleans [10] and Washington, D. C.,[11] in the United States. Although the cases were not reported in detail it is mentioned in the literature that the disease has been seen in Berlin, Vienna and in three other instances [12] in the United States.

2. Schüffner, W.: Recent Work on Leptospirosis, Tr. Roy. Soc. Trop. Med. & Hyg. **28**:7-31 (May 17) 1934.

3. Roos, C. J.; Walch-Sorgdrager, B., and Schüffner, W. A. P.: Epidemic of Leptospira Canicola Infection in Human Subjects and Dogs, Nederl. tijdschr. v. geneesk. **81**:3324-3325 (July 10) 1937.

4. Meyer, K. F.; Eddie, B., and Stewart-Anderson, B.: Canine, Murine and Human Leptospirosis in California, Proc. Soc. Exper. Biol. & Med. **38**:17-19 (Feb.) 1938.

5. (*a*) Legras, A. M., and Wolters, D. H. F.: Ophthalmologic Complications in Case of Weil's Disease Typhus Canicola, Ophthalmologica **99**:469-470 (May) 1940. (*b*) Roos, Walch-Sorgdrager, and Schüffner.[3]

6. Tetzner, E.: Serologisch sichergestellter Fall von Weilscher Krankheit —Typ Leptospira canicola—beim Menschen unter dem Bilde einer Meningitis, Klin.Wchnschr. **17**:508-509 (April 2) 1938.

7. (*a*) Brammer, E.; Petersen, C. B., and Scheel-Thomsen, A.: Case of Leptospirosis Canicolaris Related to Weil's Disease, with Review of Clinical Picture, Ugesk. f. læger **100**:419-423 (April 21) 1938. (*b*) Bukh, N.: Case of Leptospirosis Canicolaris with Marked Nephropathy, ibid. **102**:1142-1145 (Oct. 31) 1940. (*c*) Bjørneboe, M.: Two Cases of Leptospirosis Canicolaris with Serous Meningitis, ibid. **103**:1281-1286 (Oct. 2) 1941.

8. Snapper, I.; Chung, H. L.; Chu, I., and Chen, K. C.: Preliminary Observations on Human, Canine and Murine Leptospirosis in North China, Chinese M. J. **58**:408-426 (Oct.) 1940.

9. (*a*) Meyer, K. F.; Stewart-Anderson, B., and Eddie, B.: "Canicola Fever," a Professional Hazard, J. Am. Vet. M. A. **93**:332 (Nov.) 1938. (*b*) Meyer, Eddie and Stewart-Anderson.[4]

10. Bruno, F. E.; Wilen, C. J. W., and Snavely, J. R.: Spirochetal Jaundice: Report on Fifteen Cases, Including Two Cases of Leptospira Canicola Infection, J. A. M. A. **123**:519-524 (Oct. 30) 1943.

11. Tievsky, G., and Schaefer, B. G.: Canicola Fever (Leptospirosis Canicola): Report of Human Case and Review of Literature, M. Ann. District of Columbia **13**:11-16 (Jan.) 1944.

(Footnotes continued on next page)

Undoubtedly not all the cases that have been seen have been reported, and it is possible that a few cases were missed in the survey of the literature. Also, one may be sure that the disease has gone undiagnosed in an unknown number of cases. There undoubtedly have been subclinical infections when the person has not been aware of the fact that he was infected and did not consult a physician. At present it is impossible to estimate how frequently this may have occurred. Certainly one can expect more cases to be found when the medical profession is more acutely aware of the presence of this disease and when it consequently looks for it more frequently. Such was the case with Weil's disease. At any rate canicola fever is a rare disease, and its presence is not fully appreciated by the medical profession at large.

At first it was thought that L. canicola was only a variant of L. icterohaemorrhagiae by some observers.[12] At present, however, it is generally agreed that infection with L. canicola represents a distinct disease in that it varies from Weil's disease immunologically, in mortality, in its virulence on test animals and, perhaps, in some clinical aspects.

CLINICAL PICTURE

Unfortunately in many of the reports the clinical features presented by the cases are only summarized. Detailed data of the clinical features presented by each particular case are available in about a dozen instances. The number of cases reported is still much too small to offer more than generalities to one trying to define the clinical characteristics of this disease. At the beginning, however, it can be said that the clinical picture of this disease is strikingly similar to that seen in Weil's disease. As a matter of fact the diseases cannot be differentiated clinically. Generally speaking canicola fever tends to be milder than the illness caused by L. icterohaemorrhagiae.

The onset of the disease may be variable. In a large percentage of cases the onset has been sudden and stormy. Such onsets are marked by a high temperature (101 to 104 F.), pronounced malaise, chills, anorexia, myalgia and arthralgia. Abdominal distress seems to be somewhat less commonly seen than in Weil's disease. In other cases the onset is insidious. Meyer, Stewart-Anderson and Eddie [9a] stated

12. (*a*) Randall, R., and Cooper, H. K.: Golden Hamster (Cricetus Auratus) as Test Animal for Diagnosis of Leptospirosis, Science **100**:133-134 (Aug. 11) 1944. (*b*) Larson, C. L.: Experimental Leptospirosis in Hamsters (Cricetus Auratus), Pub. Health Rep. **59**:522-527 (April 21) 1944. (*c*) Greene, M. R.: Survey for Leptospirosis in Southern California, Am. J. Hyg., Sect. B **34**:87-90 (Sept.) 1941.

13. Packchanian, A.: Prevalence of Infectious Jaundice in the United States as Determined by Agglutination and Animal Innoculation Tests, Am. J. Path. **14**: 638-642 (May 4) 1938.

that L. canicola infections can easily be mistaken for influenza, undulant fever or tuberculosis. The disease can be so mild that the patient never appreciates that he has been infected and consequently does not consult a physician.[14] Roos and his associates [3] reported such cases. Serologic evidence of the disease was found in mildly ill members of a family in which another member and the family dog had outspoken clinical evidence of the disease. The presenting symptoms of the disease may be neurologic, and cases have been reported [15] when the only clinical evidence of disease was that of meningitis.

There are some clinical features seen often enough to warrant a brief discussion of each: 1. Jaundice: This classical sign, which is present in one half to two thirds of the cases of Weil's disease, was not seen in 12 cases of canicola fever reported from Holland.[15a] Generally speaking this sign has been absent from the cases reported from Europe and China, but has been seen in half of the cases reported from the United States. This is interesting in that the same approximate variation has been seen in the canine L. canicola infections reported from the different continents. The variations in the symptom complex caused by L. canicola apparently reflect variations in virulence and individual properties of different strains of this organism. This variation from strain to strain is further emphasized by the fact that some strains of L. canicola readily kill hamsters,[12a] while other strains are not so fatal.[16] Meyer, Stewart-Anderson and Eddie [17] stated that the pathogenicity of L. canicola does not parallel its icterogenic properties. 2. Nephritis: This complication of leptospiral infections is seen in canicola fever. All patients may show some mild albuminuria and cylindruria; however, this is not to be interpreted as evidence of nephritis. The Dutch investigators [15a] found no remarkable urinary changes in their 12 cases. Since that time at least 3 instances [18] of acute hemorrhagic nephritis have occurred. Azotemia occurred in 1 of the cases of Bruno, Wilen and Snavely.[10] There is no evidence that chronic nephritis has resulted in human beings from this disease. 3. Meningitis: In 4 of 12 cases reported from Holland there were meningitic signs and symptoms. Walch-Sorgdrager,[15a] in a comprehensive

14. Meyer, K. F.; Stewart-Anderson, B., and Eddie, B.: Epidemiology of Leptospirosis, Am. J. Pub. Health **29**:347-353 (April) 1939.

15. (*a*) Walch-Sorgdrager, B.: Leptospirosis, Bull. Health Organ., League of Nations **8**:143-386, 1939. (*b*) Roos, Walch-Sorgdrager and Schüffner.[3] (*c*) Tetzner.[6] (*d*) Bjørneboe.[7c]

16. Morton, H. E.: Susceptibility of Syrian Hamsters to Leptospirosis, Proc. Soc. Exper. Biol. & Med. **49**: 566-568 (April) 1942.

17. Meyer, K. F.; Stewart-Anderson, B., and Eddie, B.: Canine Leptospirosis in United States, J. Am. Vet. M. A. **95**: 710-729 (Dec.) 1939.

18. Bukh.[7b] Meyer, Stewart-Anderson and Eddie.[9a] Bruno, Wilen and Snavely.[10]

study on leptospirosis, wrote in some detail of the meningitic form of leptospiral (either with L. canicola or L. icterohaemorrhagiae) infections. The only evidence of disease may lie in meningitic signs and symptoms. Evidence of meningitis occurred in both of Snapper's cases,[8] and confusion, convulsions and delirium have been seen in other cases.

Some hemorrhagic tendency is present in almost all cases. Conjunctival injection is often present, and epistaxis is not rare. Pulmonary infiltrations are apparently somewhat less frequent than in Weil's disease.

Fever may vary considerably in type. It may be undulant, intermittent or sustained. Fever may be present for only a few days, or it may be present for weeks, even up to two months. Naturally, the duration of the disease is equally variable, and febrile relapses occur not infrequently, as is the case with Weil's disease. Cardiac involvement has been reported in only one instance,[5a] this being transient partial heart block. Tievsky and Schaefer's[11] paper contains a chart of the clinical features of this disease.

As yet there have been no deaths from canicola fever, and only 1 instance of a complication[8]—a vitreous opacity in the left eye. Convalescence may be slow and weakness may be pronounced for a considerable period after subsidence of the acute infection.

LABORATORY FINDINGS

As in Weil's disease, there is usually a leukocytosis with a predominance of polymorphonuclear cells. A mild anemia of the secondary type may develop during the disease. Generally the laboratory findings characteristic of infectious hepatitis are present. The van den Bergh reaction is of little aid and varies remarkably from case to case. In many cases the urine shows albuminuria and cylindruria of mild proportions, but in cases complicated by renal involvement the urinary findings typically seen in acute hemorrhagic nephritis are present. Rarely azotemia may develop. When meningeal signs are present there is usually a mild increase in the cerebrospinal fluid pressure. The cerebrospinal fluid is clear and usually weakly positive for albumin. There may be up to 300 white blood cells in the fluid; at first polymorphonuclear cells predominate, but soon the lymphocyte becomes the predominating cell. According to Walch-Sorgdrager[15a] the chlorides may be slightly down and the sugar slightly elevated. The cerebrospinal fluid is occasionally bloody. Leptospiras may be present in the fluid. The cerebrospinal fluid may show these characteristics in the absence of any clinical evidence of meningeal irritation.

Unlike Weil's disease, dark field examinations of the blood for leptospiras are thought to be useless. Experience is needed for accuracy

in making dark field examinations of blood for leptospiras, or else pseudospirochetes due to fibrin and degenerating blood cells described by Schultz [19] may be mistaken for them. On the other hand, leptospiras can frequently be seen in the patient's urine between the tenth and the thirtieth day of the disease if certain precautions are taken. According to Ashe and his associates [20] best results can be obtained in dark field examination of urine if the urine used is less than one hour old and approximates neutrality in reaction. L. canicola is identical morphologically to L. icterohaemorrhagiae even by electron microscope.[21] The leptospiras are 4 to 10 microns long and contain no granules, internal structure or flagellae. They may have a hook on one or both ends. All progression is in the direction of the straight end and by a rotary motion of the hooked end. If both ends are hooked there is no progression. It has been said [22] that L. icterohaemorrhagiae can be differentiated from other blood spirochetes by its insolubility in a 10 per cent solution of saponin. No data were found on the reaction of the 10 per cent solution of saponin on L. canicola.

Brown and Davis [23] described an adhesion test for the differentiation of leptospiras. A complement fixation test for the same purpose was described by Gaehtgens [24]; however, these tests are not generally used, nor are they as valuable as the agglutination-lysis test of Schüffner. They offer no additional information when they are used. The agglutination-lysis test is designed to show the presence of antibodies in the serum of the patient against the leptospiras suspected of causing the infection. With proper antigens it can be used with equal value in testing for either Weil's disease or canicola fever. According to Raven [25] seven day old cultures of L. canicola grown on Schüffner's modification of Verwoort's medium are best to employ as antigens. Some investigators claim that it is best to use live cultures, but equally good results

19. Schultz, E. W.: Pseudospirochetes Derived from Red Blood Cells, J. Lab. & Clin. Med. **8**:375-381 (March) 1923.

20. Ashe, W. F.; Pratt-Thomas, H. R., and Kumpe, C. W.: Weil's Disease: Complete Review of American Literature and Abstract of World Literature; Seven Case Reports, Medicine **20**:145-210 (May) 1941.

21. Morton, H. E., and Anderson, T. F.: Morphology of Leptospira Icterohemorrhagiae and L. Canicola as Revealed by Electron Microscope, J. Bact. **45**: 143-146 (Feb.) 1943.

22. Bertucci, E. A., Jr.: Leptospirosis, Am. J. M. Sc. **209**:86-111 (Jan.) 1945.

23. Brown, H. C., and Davis, L. J.: The Adhesion Phenomenon as an Aid to the Differentiation of Leptospira, Brit. J. Exper. Path. **8**:397-403 (Oct.) 1927.

24. Gaehtgens, W.: Die Serodiagnose der Weilschen Krankheit mittels Komplementbindungs- und Flockungs-reaktion, Ztschr. f. Immunitätsforsch. u. exper. Therap. **79**:428-451, 1933.

25. Raven, C.: Canine Leptospirosis in Pennsylvania, J. Infect. Dis. **69**: 131-137 (Sept.-Oct.) 1941.

can be obtained from freshly formalized cultures. Agglutination occurs when the antibodies are concentrated in the serum being tested, but when the end point is approached only lysis occurs. Prozone phenomena may occur. Anamnestic reactions have been reported, and false positive reactions rarely occur. A negative agglutination-lysis reaction thirty days after the onset rules out the disease. Raven's article [25] is especially recommended for information concerning the preparation of Schüffner's modification of Verwoort's medium, for the method of obtaining antiserum and for the technic of performing the agglutination-lysis test. Antibodies against L. canicola appear about the tenth day of the disease and reach their maximum about the thirtieth day. The titer may remain elevated for many years but usually falls to 1 : 300 in two to three years. There is mild cross agglutination between L. canicola and L. icterohaemorrhagiae, but there is rarely any difficulty in determining which is the offending organism. Rarely, repeated agglutinations at intervals of a few days are required to determine the causative leptospira. Since L. icterohaemorrhagiae and L. canicola are identical morphologically and since the clinical pictures of canicola fever and Weil's disease are so similar, it is impossible to differentiate between the two except by serologic means. Mild cross agglutinations between L. canicola and Leptospira hebdomadis have also been reported.[8] The article of Meyer and his associates [17] also contains useful information concerning laboratory technics. The diagnosis of canicola fever generally has been made by the agglutination-lysis test, and certainly the diagnosis always has been confirmed by it. There is no commercial antigen that gives consistently dependable results, and investigators generally prepare their own antigens. Antibodies against L. canicola may be present in the cerebrospinal fluid, but they are usually present in a lower titer than that found in the serum. Leptospiras may be found in the cerebrospinal fluid, and Fontana's stain is best used in the search for them. Levaditi's stain is used when one is searching for leptospiras in tissues.

L. canicola can be isolated from the urine if proper care is employed. It is best to use fresh, centrifuged, neutral urine for inoculation of Schüffner's modification of Verwoort's medium. Five to six weeks may be required for growth of the organism. Leptospiras apparently grow best in a narrow zone just below the surface of the medium where the oxygen tension is somewhat reduced. The optimum temperature for growth has been said to be 25 to 30 C.[22] Care must be employed in the selection of test animals to be used in the isolation of L. canicola. Rabbits, white mice, rats, field mice and cats are poor test animals. They rarely, if ever, become infected, and the leptospiras cannot be isolated form their blood. According to recent reports [26] hamsters and

26. Meyer, Eddie and Stewart-Anderson.[4] Randall and Cooper.[12a] Larson.[12b] Morton.[16]

guinea pigs are the best animals to employ. In contrast to L. icterohaemorrhagiae, L. canicola may not infect guinea pigs, and even if the guinea pigs become infected they may not become jaundiced and die (especially if there have not been repeated, serial passages). It is reported [16] that 0.5 cc. of a live culture of L. canicola injected subcutaneously into 3 to 5 week hamsters will infect the animals, and leptospiras may be found in their heart blood after forty-eight, seventy-two or ninety-six hours, although the animals survive. With L. canicola of greater virulence death of the hamsters may occur in nine to ten days.[12a] L. icterohaemorrhagiae invariably causes death in hamsters in about five days.

DIFFERENTIAL DIAGNOSIS

Naturally the differential diagnosis is the same as that of Weil's disease, since both have similar clinical pictures. This differentiation is made by serologic means. A history of exposure to contamination with dog's urine is of great value in diagnosing canicola fever. Such a history has been obtained in approximately 50 per cent of the cases reported thus far. The commonest confusion in leptospiral infections is with common infectious hepatitis. The high white blood cell count, rapid onset, absence of splenomegaly and lymphadenopathy, more rapidly appearing and deeper jaundice, hemorrhagic tendencies, meningeal, pneumonic and nephritic manifestations and a history of possible exposure to contamination with leptospiras should suggest that a patient is suffering from a leptospiral infection. Typhoid may give some difficulty in differential diagnosis, but this differentiation is made through the difference in the incubation periods of the two diseases, the absence of calf tenderness in typhoid and the absence of abnormalities of the cerebrospinal fluid in typhoid. Influenza may at times be confused with canicola fever. Yellow fever, relapsing fever, blackwater fever, syphilis of the liver, hepatic abscess and acute yellow atrophy have been included in the differential diagnosis for leptospiral infections. A lengthy discussion of the clinical variations between canicola fever and the disorders listed does not appear to be warranted, since a diagnosis of canicola fever certainly cannot be established, owing to the lack of a constant and well defined clinical syndrome, until laboratory evidence is obtained. Laboratory tests should always be run when the history or clinical features of a case suggest that L. canicola may be causing the illness.

EPIDEMIOLOGY

In approximately 50 per cent of cases it has been possible to trace the source of infection to an infected dog. Dogs infected with the disease excrete the organisms in their urine. It is generally thought that dogs exhibit leptospiruria for only a few months; however, Meyer and his

associates [14] stated their belief that a chronic nephritis may develop from the infection and cause the dog to shed leptospiras for many months. Human beings become infected by contacting broken skin or intact mucous membrane with material contaminated with living leptospiras. The organisms will not penetrate intact skin. Consequently, the disease is an industrial hazard of veterinarians and dog catchers. Children often get the disease by playing with an infected dog. There is no instance on record of transmission of the disease from one human being to another.

The incubation period of the disease is unknown; however, it is thought to be the same as that of Weil's disease, roughly one to two weeks.

Although L. icterohaemorrhagiae is known to infect many animals (dogs, field mice, cats, pigs, foxes, mongooses, poultry, bandicoots, horses and rats [22]), L. canicola has never been shown to infect any animal naturally but the dog. The dog, nevertheless, is capable of carrying L. icterohaemorrhagiae, leptospira hebdomadis (in Java) and the Australian type of Leptospira "Ballico" in Celebes.[17]

It is known that leptospiras are capable of surviving and remaining virulent for a period of three weeks in stagnant water that has a reaction that approaches neutrality.[22] The organisms normally die at a p_H below 6.7. There is a nonvirulent type of leptospira, Leptospira biflexa, which is similar to L. icterohaemorrhagiae and L. canicola morphologically. Some investigators have suggested that under proper conditions a nonpathogenic leptospira, such as L. biflexa, may change into a pathogenic leptospira, such as L. icterohaemorrhagiae or L. canicola. Bertucci [22] stated that Inada believes an infective, granular form of leptospira exists.

Leptospirosis canicola is a common and serious disease in dogs. Generally speaking, 4 to 15 per cent of dogs the world over have a titer against L. canicola of 1 : 100 or over. Much higher values have been obtained. Twenty-five per cent of Northern California dogs [17] gave positive agglutinations to L. canicola, and 19 per cent of the dogs of Southern California,[12c] while 38.1 per cent of 105 rural dogs from Pennsylvania had agglutination titers to L. canicola of 1 : 300 or better.[25] It is known that the perecentage of positive titers to L. canicola increases with the age of the dogs tested. About 90 per cent of dogs over 6 years of age have positive reactions to L. canicola. More males are infected than females, and this is possibly due to the habit of male dogs of sniffing the genitals of other dogs. There is evidence to suggest that the disease can be transmitted from one dog to another by intercourse. There are more dogs infected with L. canicola than with L. icterohaemorrhagiae. Raven [25] gave a table of the prevalence of canine leptospirosis the world over.

The disease in dogs has been called Stuttgart's disease or dog typhus. According to Meyer and his associates [14] the disease may take two forms in dogs. There may be considerable hepatic damage with jaundice, "the yellows" (33 per cent of cases), or there may be an extreme hemorrhagic gastroenteritis without jaundice, Stuttgart's disease (34 per cent of cases). In some cases both types of the disease are seen in the same dog at different stages of the disease. Dogs are more likely to become jaundiced when infected with L. icterohaemorrhagiae than with L canicola; however, they are more likely to die in uremia if the infecting organism is L. canicola. The mortality in dogs has been said to be as high as 50 to 80 per cent, but this certainly does not include many cases of mild disease which undoubtedly occur. The fact that many subclincal cases in dogs occur is supported by the high percentage of dogs which are serologically positive to L. canicola and by the fact that experimental efforts to infect dogs have produced only subclinical infections.

There is undoubted evidence, as already stated, that subclinical cases of canicola fever occur in human beings. One would, therefore, expect routine agglutinations to demonstrate a certain percentage of persons with agglutinins in their serum against L. canicola. This has not been the case in the studies so far carried out. Tiffany and Martorana [27] found no titers against L. canicola in the serums of 59 persons whose activities were such as to bring them into contact with dogs. Greene [12c] found the serums of 426 persons who had close contact with dogs to have no antibodies against these leptospiras. Although the percentage of rats infected with L. icterohaemorrhagiae is roughly the same as the percentage of dogs infected with L. canicola, a small but definite percentage of the entire human population have titers against L. icterohaemorrhagiae, although they may not recall ever having had symptoms of Weil's disease. This percentage becomes remarkably high when the persons tested are rat catchers, fish workers, and the like—sometimes approaching 50 per cent. This variation is partly explainable in that food and water are not so frequently contaminated by dogs as by rats. Also, rats shed leptospiras for the rest of their lives once they are infected, whereas it seems that dogs are relatively transient shedders of L. canicola. The fact that the urine of a dog is usually rather acid in reaction, and thus will tend to kill leptospiras, may also help to explain the rarity of canicola fever. It may be, however, that once canicola fever becomes better recognized it will me found more often.

Preventive measures, such as acidification of stagnant water, as used against Weil's disease are not practical against canicola fever since so

27. Tiffany, E. J., and Martorana, N. F.: Leptospirosis in New York City: Serological Survey, Am. J. Hyg. **36**:195-204 (Sept.) 1942.

few cases have been reported. It is necessary, however, to isolate an infected dog until he stops showing leptospiras in his urine. It also is likely that more cases of canicola fever would be discovered if members of a family possessing a dog infected with L. canicola were routinely tested for antibodies in their serums.

TREATMENT

In the past the treatment of canicola fever has been the same as that used in any acute infectious hepatitis—namely, symptomatic therapy and dietary and vitamin therapy designed to protect the liver. No specific therapeutic agents have been used with success in the disease in human beings. Sulfonamide compounds have been shown experimentally and clinically to have no effect against either Weil's disease or canicola fever. Arsenicals are dangerous and ineffective. There is some evidence to indicate that penicillin will prove useful in the treatment of both these diseases. Recently Alston and Broom [28] showed that penicillin had both lethal and inhibitory effects in vitro on nine strains of L. icterohaemorrhagiae and one strain of L. canicola. It cured leptospirosis icterohaemorrhagica in guinea pigs if given early and in large doses; however, the drug did not prevent the development of antibodies against the leptospiras. It is suggested that penicillin would have the same effect against leptospirosis canicola in animals. There are a few reports in the literature [29] of Weil's disease treated with penicillin, and in general it seems that penicillin is useful if given in large doses early in the disease. It would appear likely that penicillin would have the same effect on canicola fever if the same conditions were met. Bismuth compounds have been used on the Continent [30] with apparently good results. There is no instance of their being used against canicola fever.

Although antiserum against L. icterohaemorrhagiae infections in man has been used with success abroad,[31] no similar antiserum has been used against canicola fever. L. canicola antiserum [17] has given striking success in the disease in dogs if given early in the course of the disease.

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28. Alston, J. M., and Broom, J. C.: Action of Penicillin on Leptospira and on Leptospiral Infections in Guinea Pigs., Brit. M. J. **2**:718-719 (Dec. 2) 1944.

29. Carragher, A. E.: Case of Weil's Disease Treated with Penicillin, Brit. M. J. **1**:119 (Jan. 27) 1945. Bulmer, E.: Weil's Disease in Normandy: Its Treatment with Penicillin, ibid. **1**:113-114 (Jan. 27) 1945.

30. Uhlenhuth, P., and Seiffert, A.: Untersuchungen über die Ausheilung der Weilschen Krankheit bei Meerschweinchen unter der Behandlung mit Bismuto-Yatren A, Zentralbl. f. Bakt. (Abt. 1) **114**: 241-251 (Oct. 31) 1929.

31. Inada, R.: Prophylaxis and Serum Treatment of Spirochaetosis Icterohemorrhagiae, Japan M. World **2**:189-193 (July) 1922. Walch-Sorgdrager.[15a]

Human beings have been vaccinated against Weil's disease [32] with homologous vaccine with definite benefit. No such attempt has been made against canicola fever because of its rarity. Animals can certainly be protected against L. icterohaemorrhagiae if they are inoculated with killed or nonvirulent L. icterohaemorrhagiae. Some investigators say that there is no cross protection between L. icterohaemorrhagiae and L. canicola,[33] while others [34] claim that there is.

It can be said that whatever specific treatment that is used against canicola fever should be given early. At present most of the diagnoses are made serologically, and consequently late in the course of the disease. It is unlikely that any specific therapy will be of value until the presence of the disease is appreciated sufficiently by the medical profession so that a diagnosis will be made early.

SUMMARY

A case of canicola fever, or leptospirosis canicola, is reported. The literature is reviewed relative to the history, incidence, clinical features, laboratory findings, epidemiology and treatment of the disease.

32. Das Gupta, B. M.: Observations on Some Immunological Aspects of Leptospira Icterhemorrhagiae: Development of Active Immunity in Many Following Injection of Leptospira Vaccine, Indian M. Gaz. **77**: 28-29 (Jan.) 1942.

33. Larson, C. L.: Protection Test in Mice for Indentification of Leptospira Icterohemorrhagiae (Weil's Disease), Pub. Health Rep. **56**:1593-1609 (Aug. 8) 1941.

34. Smith, J.: Vaccination of Guinea-Pigs and Human Beings Against Leptospiral Infections, J. Hyg. **37**:261-270 (April) 1937.

CLINICAL ASPECTS OF CALCIFICATION OF THE MITRAL ANNULUS FIBROSUS

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CALCIFICATION of the mitral annulus fibrosus has been studied by pathologists [1] and is fairly often discovered more or less accidentally during life by radiologists.[2] Both groups of observers, properly enough, have regarded it as a degenerative change of no clinical significance.

Yet such calcification is not entirely without clinical interest and was in part the subject of a recent monograph.[3] Its occurrence in the older age groups guarantees that it will be associated at least now and then with obvious heart disease [4]; in fact, it has long been known [5] as one variety of those calcifications which cause heart block.[6]

From the Department of Medicine, Stanford University School of Medicine, San Francisco.

1. (*a*) Geerling, J. G.: Sclerosis annularis valvularum, Thesis, Groningen, Leeuwarden, B. B. Westerhuis, 1929. (*b*) Giese, W.: Die Verkalkungen des Herzskeletts, Beitr. z. path. Anat. u. z. allg. Path. **89**:16-39, 1932. (*c*) Ribbert, H.: Die Erkrankungen des Endokards, in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1924, vol. 2, p. 184. (*d*) Martens, G.: Beziehungen zwischen der Verkalkung des Annulus fibrosus der Mitralklappen und anderen regressiven Erscheinungen, Beitr. z. path. Anat. u. z. allg. Path. **90**:497-502, 1932.

2. (*a*) Sosman, M. C.: The Technique for Locating and Identifying Pericardial and Intracardiac Calcifications, Am. J. Roentgenol. **50**:461-468 (Oct.) 1943; (*b*) Sosman, M. C.: Subclinical Mitral Disease, J. A. M. A. **115**:1061-1066 (Sept. 28) 1940. (*c*) Sundberg, C. G.: Kymographische Untersuchung eines Herzens mit verkalktem Annulus fibrosus, Acta radiol. **22**:834-840, 1941. (*d*) Roesler, H.: Clinical Roentgenology of the Cardiovascular System, ed. 2, Springfield, Ill., Charles C Thomas, Publisher, 1943, p. 265.

3. Menezes de Oliveira, R.: Escleroses valvulares calcificadas, Rio de Janeiro, Tipografia do Patronato, 1943; reviewed, Am. Heart J. **29**:139 (Jan.) 1945.

4. Marks, J. H.: Calcification in the Annulus Fibrosus of the Mitral Valve, New England J. Med. **214**:411-414 (Feb. 26) 1936.

5. Cowan, J., and Ritchie, W. T.: Diseases of the Heart, ed. 2, London, Edward Arnold & Co., 1922, p. 122.

6. Yater, W. M., and Cornell, V. H.: Heart Block Due to Calcareous Lesions of the Bundle of His: Review and Report of a Case with Detailed Histopathologic Study, Ann. Int. Med. **8**:777-789 (Jan.) 1935.

Then too either the calcification itself or the accompanying valvular changes of aging might reasonably be expected to alter cardiodynamics even in the absence of heart block; practically nothing [7] has been written about murmurs in its presence, and prominent authors [8] dismiss it somewhat vaguely as occasionally associated with mitral regurgitation and an apical systolic murmur.

The primary purpose of this paper is to present observations made during the lives of 10 elderly patients with calcification of the mitral annulus fibrosus; our own interest in this disorder was aroused by the heart block found in the electrocardiograms of 5 of these patients and by the nature of the murmurs heard in their hearts.

REPORT OF CASES

CASE I.—Mrs. M. L. was 74 years of age when dyspnea brought about her admission to Stanford University Hospitals on May 30, 1938. She had never had rheumatic fever but had been told of the presence of a murmur when she was 56.

She was small, dyspneic and orthopneic. Signs of moderate passive congestion were present. The arterial pressure averaged about 200 mm. during systole and 90 mm. in diastole. The heart was enlarged some 2 cm. to the left, and its beats were regular at a rate of 45 per minute. A loud rather coarse systolic murmur, best heard along the left sternal border from the second to the fifth rib, was transmitted to the apex as well as to the aortic area and the carotid arteries; there was no thrill. The apical first sound varied in intensity.

Auricular sounds heard at the apex were at first thought to be the usual sounds audible in patients with complete heart block; later they were discovered to be murmurs (see third paragraph following).

An electrocardiogram showed complete heart block and left bundle branch block. Roentgenograms showed pulmonary congestion, much calcification in the aorta and moderate cardiac enlargement.

Improvement followed rest in bed and the use of diuretics, sedatives and digitalis. In the electrocardiograms, the bundle branch block soon disappeared, not to return until 1941; sinus rhythm was recorded three times in June and July of 1938, with P-R intervals of 0.19, 0.20 and 0.21 second; the supernormal phase of conduction (P-R, 0.16 second) was present once in the same period; later 2:1 block was present almost as often as complete block, and auricular fibrillation appeared for two months in 1941. The Stokes-Adams syndrome never occurred. Most of the time the patient sat up at home and was even ambulatory. Edema returned in 1941 but was controlled by mercurial diuretics. She died soon after the occurrence of clonic movements in the right arm and leg on July 2, 1943, at the age of 79; permission for necropsy was refused.

When the patient came to the laboratory in 1939 for the purpose of having the heart sounds in complete block recorded, Dr. J. K. Lewis pointed out during

7. Libman, E., in discussion on McGinn, S., and White, P. D.: Valvular Atherosclerosis, Am. Heart J. **10**:404-405 (Feb.) 1935.

8. (*a*) Levine, S. A.: Clinical Heart Disease, ed. 3, Philadelphia, W. B. Saunders Company, 1945, pp. 39 and 227. (*b*) Osler, W.: Principles and Practices of Medicine, edited by H. A. Christian, ed. 15, New York, D. Appleton-Century Company, Inc., 1944, p. 1052.

auscultation that the apical sound heard during ventricular diastole was in reality a murmur. This was confirmed by a phonocardiogram (fig. 1 *A*), which showed the relation of the murmur to the P wave; the murmur with ventricular systole and the variation in intensity of the first heart sound were also demonstrated.

The murmur confined to the apex was best heard with the patient recumbent, particularly in the left lateral position. It was of blowing quality and never loud although readily audible. Varying greatly in intensity, it was faintest just before ventricular systole and loudest during a period near early ventricular diastole. When 2:1 block was present, the murmur was heard only with the blocked auricular systole and was scarcely recorded with the conducted one (P-R, 0.24

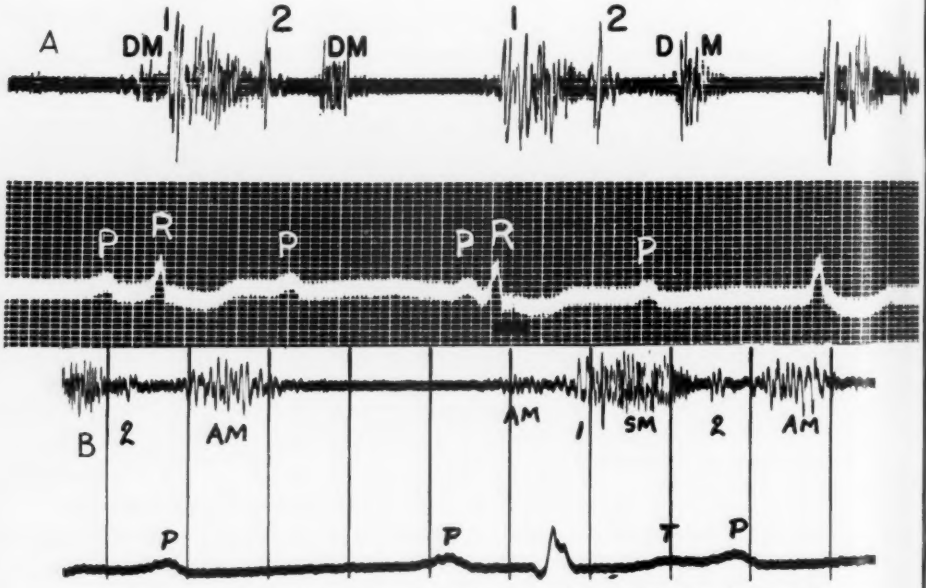

Fig. 1.—*A* (case 1), heart sounds at the apex with simultaneous electrocardiogram in the presence of complete auriculoventricular block. *DM* designates the murmur with auricular activity and *1* and *2* the first and second heart sounds. Short black bar locates maximum vibrations of an intense first sound with short P-R interval. (Time markings in all phonocardiograms are 0.04 and 0.20 second). *B* (case 2), heart sounds at the apex (above) with simultaneous electrocardiogram. *AM* designates auricular murmur, *SM* the murmur with ventricular systole and *1* and *2* the first and the second heart sounds.

second); with auricular fibrillation, the murmur was audible and recorded early in diastole.

Fluoroscopic examination with Dr. Edward Leef in November 1939 showed the heart to be smaller than before and of practically normal size; the left auricle was not prominent, and a nearly complete ring of calcification was seen in the region of the mitral annulus fibrosus, moving toward the apex with ventricular systole. The calcification was visible in films. These observations were later repeatedly confirmed.

Summary.—A woman of 74 was found to have congestive heart failure and complete auriculoventricular block. There was a loud, coarse murmur, best heard at the left sternal border with ventricular systole; there was also a fainter apical blowing murmur with auricular activity. Calcification of the mitral annulus fibrosus was seen with the fluoroscope and in roentgenograms, but there was no enlargement of the left auricle. Meanwhile, complete heart block temporarily gave way at various times to sinus rhythm with normal conduction and to 2:1 block; it was at times complicated by left bundle block and by auricular fibrillation. With the latter, the apical murmur was found in early diastole. Congestive failure was controlled with diuretics and digitalis. The patient died at the age of 79 of cerebral vascular disease.

CASE 2.—Mr. P. B. was 65 when he first visted Stanford Out-Patient Clinics, March 25, 1940, because of dyspnea and angina pectoris. He had not had rheumatic fever but had known of a murmur for years.

Examination showed a large man who did not appear to be ill. There were no signs of congestive failure. There was only moderate thickening of the radial arteries, and the retinal vessels were practically normal. The arterial pressure was 135 mm. in systole and 90 mm. during diastole. The heart was not enlarged. The beats were regular at a rate of 84 per minute. Over the precordium, loudest at the base, was heard a fairly loud, rough systolic murmur; diastole was clear. No thrill was felt. The electrocardiogram showed sinus rhythm, P-R interval of 0.22 seconds and left axis deviation with normal T waves.

The patient's symptoms improved with the use of glyceryl trinitrate and phenobarbital. A year later the conduction time was only 0.18 second. In March 1943 he again became dyspneic; digitalis was administered in the usual dosage when basal rales were heard. Two weeks later complete heart block was present temporarily, followed by 3:2 auriculoventricular block.

On examination, March 24, 1943, one heard a loud, rough murmur with ventricular systole, best at the base, but transmitted to the carotid arteries and to the apex; there was also a fainter rough blowing murmur at the apex with auricular activity, loudest when that event occurred early in ventricular diastole (fig. 1 *B*). The apical first sound varied in intensity from cycle to cycle. Fluoroscopic examination repeatedly showed a densely calcified ring in the region of the mitral annulus fibrosus; this was recorded in films. The left auricle was not dilated; the heart was slightly enlarged.

With smaller amounts of digitalis, sinus rhythm returned but with P-R intervals of 0.23 to 0.32 second; with such prolonged conduction times which persisted even during the temporary withdrawal of digitalis, the apical murmur was found only in late ventricular diastole.

In 1944 and 1945 congestive failure and auricular fibrillation appeared, and the heart and its left auricle enlarged. With this arrhythmia, the apical murmur became fainter, was not audible except when the patient was in the recumbent position and was confined to early diastole. The patient died of congestive failure on June 2, 1945; permission for necropsy was refused.

Summary.—A man of 68 with mild congestive failure and angina pectoris had a loud, rough precordial systolic murmur; the slightly prolonged conduction time later became normal temporarily. When digitalis was followed by complete heart block, an apical murmur related to auricular activity was heard and recorded. The heart was slightly enlarged but the left auricle was not dilated at the time of the fluoroscopic examinations in which a calcified mitral annulus fibrosus was seen. With less digitalis and even without it, complete heart block was replaced

by sinus rhythm with prolonged conduction time; under these conditions the apical murmur was present only late in diastole. Congestive failure finally increased, in spite of the use of digitalis: The heart and its left auricle became dilated, and auricular fibrillation appeared, whereupon the apical murmur diminished in intensity and was confined to early diastole. The patient died at the age of 70, of congestive heart failure.

CASE 3.—Mrs. L. B. was 68 years of age when she entered San Francisco Hospital in 1939 for dyspnea on exertion; the complete heart block found at that time persisted throughout the rest of her life.

In 1941 we examined her because of dizziness on turning the head from side to side. There was no history of rheumatic fever. She was alert, elderly and slightly obese. There was evidence of peripheral and retinal arteriosclerosis. Arterial pressure was 270 mm. in systole and 110 mm. in diastole. The lungs were clear. The heart beats were regular at a rate of 48, and the heart was enlarged to the anterior line. A thrill at the base corresponded to a loud systolic murmur there, transmitted to the apex and into the carotid arteries. The first

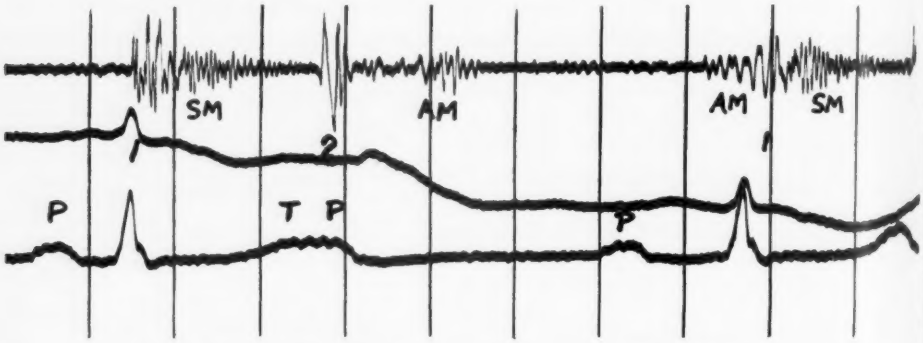

Fig. 2 (case 3).—Heart sounds at the apex (above) with simultaneous electrocardiogram (below) during complete auriculoventricular block. Ignore the irregular middle tracing. *AM* designates the murmur with auricular activity, *SM* the murmur with ventricular systole, *1* and *2* the first and the second heart sounds. Note the absence of auricular murmur after the first P wave, with P-R interval of only 0.20 second.

heart sound varied in intensity. There was a soft blowing apical murmur heard during ventricular diastole, especially early in diastole and particularly with the patient in the left lateral recumbent position; phonocardiograms (fig. 2) showed this murmur to be related to the P wave.

Roentgenograms revealed an enlarged heart, with no particular left auricular dilatation, and calcification of the mitral annulus fibrosus (fig. 3).

Angina pectoris began in May 1942, and the patient died of myocardial infarction four months later.

At necropsy, performed in the department of pathology of Stanford University, the heart weighed 420 Gm. The wall of the left ventricle was extremely thick, and there was a region of myocardial infarction posteriorly. The coronary arteries showed moderate diffuse sclerosis and narrowing without demonstrable acute occlusion. The aortic, the pulmonary and the tricuspid valves were normal. There was extensive calcification of the mitral valve ring forming a rigid band

about 1 cm. in thickness and 9 cm. in circumference (fig. 4 *A*), which extended into the bases of the cusps and there caused some distortion; near their free margins, however, the leaflets were normal. The chordae tendineae were normal. There was slight, diffuse endocardial thickening of the left auricle but no striking dilatation. The calcified mass extended well into the posterior part of the membranous portion of the interventricular septum.

There was pronounced aortic atherosclerosis. The orifices of the innominate and the left carotid arteries were nearly occluded by a gray firm mass, about 2 cm. long, adherent to each vessel wall (fig. 4 *B*). There were two scars of old healed duodenal ulcers.

Microscopic examination showed the near occlusion of these aortic branches to be due to extensive intimal thickening. The thickened area showed consider-

Fig. 3 (case 3).—A roentgenogram of the chest, oblique view, showing calcification of the mitral annulus fibrosus (not to be confused with that of the cartilages of the ribs).

able fibrous tissue and much calcium, covered by a layer of intima. The endocardium of the left auricle was thickened. The aortic valve leaflets were slightly thickened by collagenous fibrous tissue; the mitral leaflets contained small flecks of calcium in addition to being similarly thickened. Pulmonary and coronary arteries contained calcified intimal plaques; the coronary lumens were small. Calcification in the mitral annulus fibrosus destroyed much of the underlying muscle, including some of that forming the interventricular septum. In the latter region the small arteries showed extensive arteriosclerosis but no actual occlusion. No Aschoff bodies were seen.

Summary.—A woman with mild congestive failure and complete heart block for three years died at the age of 72, after myocardial infarction. An apical mur-

mur related to auricular activity was recognized as such and recorded. The calcified mitral annulus fibrosus found at necropsy was seen in roentgenograms; the calcification invaded the interventricular septum and distorted the bases of the mitral leaflets. A thrill and murmur occurred at the base with ventricular

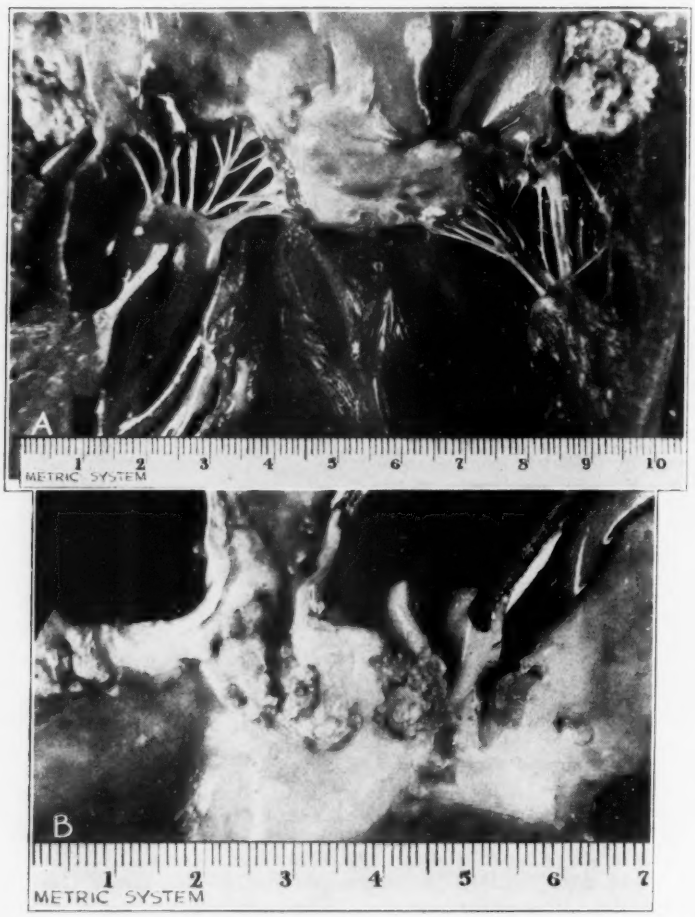

Fig. 4 (case 3).—*A*, a region of the mitral valve, with cross sections of the calcified lesion near the upper corners. *B*, lesions in the opened aorta and the innominate and left carotid arteries.

systole. Massive calcifications were found in the greatly thickened intima of the innominate and left carotid arteries; the aortic valve was virtually normal.

CASE 4.—Miss R. A. was a tiny woman of 73, in 1936, when dyspnea led to the discovery, at the Laguna Honda Home, of complete heart block. She had never

had rheumatic fever. The tibias were much bowed with osteitis deformans, and she was partially deaf and blind. Moderate edema of the legs was the only sign of congestion. Peripheral arteriosclerosis was advanced. The arterial pressure was 220 mm. in systole and 70 mm. in diastole. The heart, with regular beats at a rate of 46 per minute, was enlarged to the anterior axillary line. A moderately loud, rough systolic murmur was heard over the precordium, loudest along the left sternal border; there was no thrill.

Rest and digitalis brought improvement. There were no signs of heart failure when the patient was first examined by one of us, in 1942. At that time, heart block was still complete, but cardiac enlargement was not striking. The first heart sound varied in intensity and was followed by a rough systolic murmur, moderate at the left sternal border, faint at the apex and not heard over the carotid artery. During early diastole a short blowing murmur of moderate intensity was audible at the apex; later, in other cycles, it was fainter.

Electrocardiograms showed complete heart block and left axis deviation. Careful radiologic search for intracardiac calcification was not successful. The heart was somewhat enlarged, but there was no dilatation of the left auricle.

Another physical examination, in 1944, revealed similar conditions. Phonocardiograms confirmed the auscultatory signs. Early in ventricular diastole the vibrations of a murmur accompanied auricular activity, while in late diastole there were only small vibrations of uncertain nature. Once again, a thorough roentgenologic study failed to demonstrate calcification.

Still living at Laguna Honda Home, in 1945, at the age of 82 and without cardiac complaints, the patient was temporarily transferred to the San Francisco Hospital for the purpose of demonstrating her physical signs. On this occasion, Dr. Charles E. Grayson succeeded in satisfying himself and several others, at the time of fluoroscopic examination, of the presence of calcification almost completely encircling the mitral annulus fibrosus; the lesion was visible in at least one roentgenogram. The heart was moderately enlarged, and the left auricle was thought to be prominent.

Physical examination showed that the apical diastolic murmur had become rather rumbling; it was present even when the patient sat upright but was louder when she was in the recumbent position. It was not heard more than once in each cycle and was louder early in diastole. Late in diastole a faint double auricular sound was sometimes audible, and there was an occasional loud click when auricular activity coincided with ventricular systole. The previously noted murmur of the latter event was inconspicuous. There were no signs of congestive heart failure.

Summary.—A small woman has been observed for nine years after the onset of complete heart block at the age of 73. Congestive failure, present at first, virtually disappeared. There was only a faint murmur with ventricular systole, loudest at the left sternal border. At the apex, in diastole, a murmur was heard and recorded in phonocardiograms; blowing at first, it became rumbling as time passed. It was louder when early in diastole and faint in the middle of diastole and was represented only by a faint double sound late in diastole. Roentgenographic study was not successful in showing calcification of the mitral annulus fibrosus until recently; the heart has been moderately enlarged, and the left auricle may be increasing in size.

CASE 5.—Mrs. L. T., aged 72, entered Stanford University Hospitals early in 1942 because of dyspnea for three months. There was no history of rheumatic fever. In 1919 she received antisyphilitic treatment because of a gumma and a

positive blood Wassermann reaction. In 1939 the Wassermann reactions of the blood and spinal fluid were negative. Congestive heart failure began with an infection of the upper part of the respiratory tract.

On examination the patient was obese and dyspneic. Rales were heard at the bases of the lungs. The heart was moderately enlarged; the rate of its beats varied abruptly between 34 and 104 per minute several times, and Stokes-Adams attacks occurred. Most of the time complete heart block was present. A fairly loud, rough murmur was heard at the base with ventricular systole, not transmitted into the carotid arteries but audible at the apex; there was no thrill. Auricular sounds were heard at the apex and the lower left sternal border during periods of heart block, but they were not interpreted as murmurs. In phonocardiograms, auricular activity was sometimes associated with sounds, less often

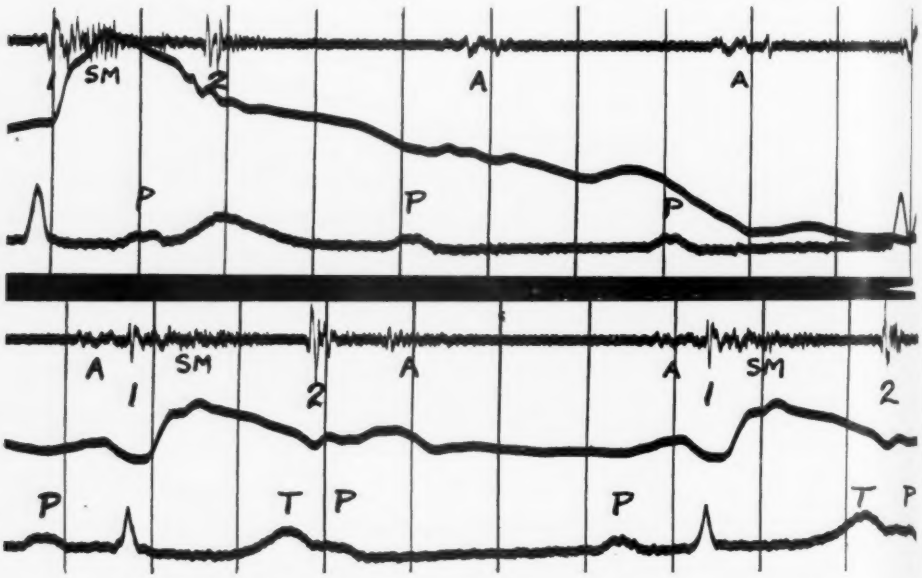

Fig. 5 (case 5).—Phonocardiograms during complete auriculoventricular block (above) and 2:1 block (below). Ignore the central vascular pulsations in each strip. In the upper record the auricular vibrations (*A*) resemble those of sounds; in the lower record they approach the appearance of a murmur, but the only audible murmur was that with ventricular systole (*SM*).

with vibrations which might be interpreted as murmurs (fig. 5). Arterial pressure was 170 mm. during systole and 100 mm. in diastole.

Roentgenograms revealed cardiac enlargement without particular auricular dilatation; calcification of the mitral annulus fibrosus was not discovered. Electrocardiograms showed 2:1 block, complete auriculoventricular block and varying bundle branch block.

Diuretics, propadrine hydrochloride and digitalis were given. Congestive failure improved, and after a month sinus rhythm reappeared, with a P-R interval of 0.20 second in each of seven records taken in the next three months. The patient left the hospital but returned seven months later with severe congestion.

Electrocardiograms showed complete heart block and left bundle branch block, and auricular tachycardia was recorded just before death, on Nov. 15, 1942.

At necropsy, performed in the department of pathology of Stanford University, the heart weighed 560 Gm. The wall of the left ventricle was thick, and there was no myocardial infarction. The coronary arteries were patent, with only a few atheromatous plaques. There was a small area of calcification at the free edge of the anterior cusp of the tricuspid valve. Similar small nodules were found at the free edges of the cusps of the aortic and pulmonary valves, which were otherwise normal. The mitral annulus fibrosus was completely calcified by a ring 0.5 cm. in thickness and 9 cm. in circumference, from which several nodules of calcified material encroached on the membranous portion of the interventricular septum; the chordae tendineae were slightly thickened. There were many calcified nodules along the proximal surface of the mitral cusps near the ring. There was some calcification at the other side of the membranous septum. The auricles were not particularly dilated.

The arch of the aorta was dilated and roughened as if by syphilis and, in addition, presented a large amount of atheromatous sclerosis. The orifices of the innominate and left subclavian arteries were slightly occluded by rough granular deposits of calcium, which differed from the calcified atheromatous plaques. The thoracic aorta was atheromatous without calcification, but the abdominal aorta was calcified as well. There was a scar of an old duodenal ulcer.

Microscopic examination showed calcification of the lowermost part of the membranous septum, with extension of dense fibrous strands among the muscle fibers of the muscular septum. There were deep infiltrations of fat and many large deposits of calcium in the aortic intima. Scar tissue frequently and abruptly replaced elastic tissue in the aorta. The adventitia of the aorta was thickened, but no cellular infiltration was found about the vasa vasorum. No Aschoff bodies were seen.

Summary.—A woman of 72, treated for syphilis, entered the hospital in a state of congestive failure, of which she later died. The heart was enlarged. Its rhythm frequently changed; 2:1 block, complete block, sinus rhythm and complete block again were recorded. Both left and right bundle branch block and, terminally, auricular tachycardia complicated complete heart block. There was a fairly loud, rough systolic murmur at the base with ventricular systole, transmitted to the apex but not into the carotid arteries. Auricular sounds were audible but never were clinically interpreted as murmurs, although phonocardiograms occasionally revealed them as prolonged vibrations. Stokes-Adams attacks were observed. At necropsy there was a calcified mitral ring (not discovered roentgenologically) from which nodules encroached on the membranous portion of the interventricular septum. Small calcified nodules were present on the free edges of cusps of the aortic, pulmonary and tricuspid valves. The left auricle was normal. There was doubtful syphilis but definite atheromatous calcification of the aorta; the orifices of the innominate and left subclavian arteries were slightly occluded by calcified deposits.

Case 6.—Mrs. A. S. was 58 years old when she first entered Stanford University Hospitals, in 1937, because of dyspnea. There was no history of rheumatic fever. Dyspnea began in 1931, following "bronchopneumonia," and continued until her death in 1943; she was bedridden most of the time. Repeated examinations showed varying degrees of congestive heart failure, always with rales at the bases of the lungs and often with universal rales and wheezes. The arterial pressure was 220 mm. in systole and 120 mm. in diastole, and there was

moderate peripheral arteriosclerosis. The heart was greatly enlarged but with regular beats at rates of 80 to 100 per minute. There was a loud, rough systolic murmur at the base and the apex, loudest at the left sternal border near the third rib; no diastolic murmur was heard or recorded in phonocardiograms, and there was no thrill. A gallop sound was often heard at the apex, and sometimes pulsus alternans was present. Heart block never occurred.

Electrocardiograms always showed sinus rhythm, P-R interval of 0.14 to 0.17 second and QRS duration of 0.08 to 0.09 second, left axis deviation and abnormal T waves, without much change through the years. Roentgenograms showed progressive cardiac enlargement, calcification of the mitral annulus fibrosus and diffuse pulmonary densities radiating from pulsating rounded hilar masses.

At necropsy, in the department of pathology of Stanford University, the heart weighed 640 Gm. and was enlarged in all chambers. There were two tiny adhesions between cusps of the aortic valve, and there was calcification at the base of this valve, with normal free edges. The tricuspid and pulmonary valves were normal. The flaps of the mitral valve and the chordae tendineae were normal except for several flat yellow atheromas on the anterior leaflet. In the mitral ring by the posterior leaflet there was a calcified mass, 3 cm. long and 0.5 cm. thick, which stopped abruptly at the margin of this cusp. One end of the calcified strand was 1 cm. from the uninvolved membranous septum.

There was moderate atherosclerosis of the aorta, with only slight involvement of the coronary arteries. The lungs were fibrotic and emphysematous; all the larger branches of the pulmonary artery were extremely dilated and atherosclerotic.

Microscopic examination showed diffuse myocardial fibrosis and atherosclerosis of the large vessels. The base of the mitral leaflet previously mentioned was fibrotic and calcified, but the cusp itself was practically normal. No Aschoff bodies were seen.

Summary.—A woman aged 64, died after twelve years of congestive heart failure, in which both systemic and pulmonary hypertension played a part. Heart block was not observed. There was a loud, rough systolic murmur over the base and the apex, but diastole was clear. Calcification of the mitral annulus fibrosus was seen in roentgenograms and confirmed at necropsy; the membranous septum was not involved.

Case 7.—Miss J. M. was only 57 when she first came to Stanford University Out-Patient Clinics in 1917, with mild hyperthyroidism, which was treated successfully with potassium iodide and irradiation. At that time arterial pressure was 175 mm. during systole and 100 mm. during diastole. The heart was not enlarged, and no murmurs were heard. An electrocardiogram showed sinus rhythm, heart beats at the rate of 100 per minute and left axis deviation.

The patient reappeared in 1933 because of weakness. The thyroid gland displaced the trachea. The cardiac findings were unchanged, but in a roentgenogram the mitral annulus fibrosus was calcified.

She disappeared, to return again, in 1944, at the age of 84, with a carcinoma of the left breast. Arterial pressure was 150 mm. in systole and 90 mm. in diastole. There was no cardiac enlargement. The heart beats were regular at a rate of 80 per minute. There was a loud systolic murmur at the left sternal border near the fourth rib but no thrill. There was no diastolic murmur by auscultation and phonocardiograms showed a few presystolic vibrations (fig. 6). Roentgenograms revealed no changes in the calcified mitral ring and no cardiac enlargement (fig. 7).

An electrocardiogram showed sinus rhythm, P-R interval of 0.15 second, QRS duration of 0.07 second and left axis deviation; it was practically identical with one made in 1917.

Fig. 6 (case 7).—Heart sounds at apex; presystolic vibrations are present, but no murmur was heard. The vibrations in this case are more prominent than those in cases 6, 8, 9 or 10.

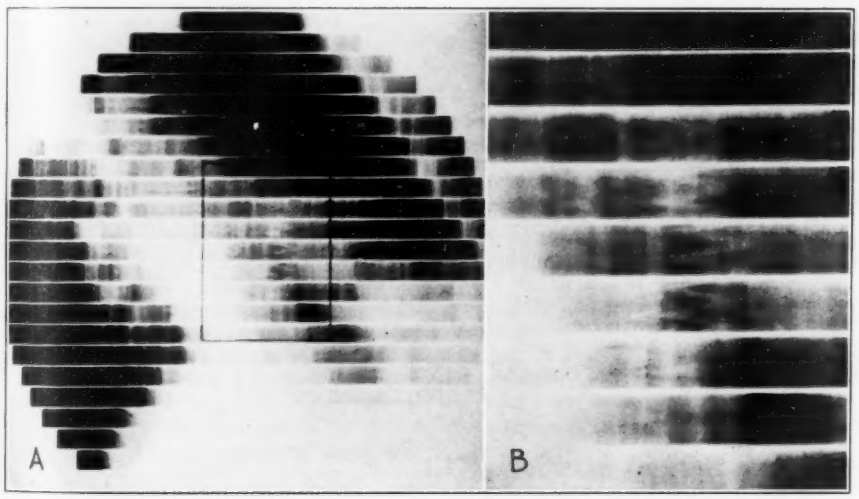

Fig. 7 (case 7).—*A*, a roentgenkymogram in the anteroposterior aspect with the patient standing and grid 45 degrees from horizontal. A rectangle outlines the area (*B*) in which movement of the calcified mitral annulus fibrosus is visible. *B*, movement of the calcified mitral annulus fibrosus; the area is that of the rectangle in *A*.

CASE 8.—Mrs. C. B. came to the Stanford University Out-Patient Clinics in 1944, at the age of 61, because of abdominal pain. Her husband had dementia paralytica. Her blood gave a positive Wassermann reaction but her spinal fluid did not. Arterial pressure was 150 mm. in systole and 90 mm. in diastole. The

heart beats were regular, with a rate of 88 per minute, the heart was not enlarged. There was a transitory and faint systolic murmur all over the precordium, loudest at the left sternal border. Diastole was clear. No murmurs were recorded in phonocardiograms, even when the heart rate was slowed to 50 beats per minute by pressure on the carotid sinus during the administration of digitalis.

An electrocardiogram showed sinus rhythm with P-R interval of 0.14 second, QRS duration of 0.07 second, left axis deviation and normal T waves. Occult blood was found in the stool, and there was slight anemia. During fluoroscopic examination, which revealed irregularity of the duodenal cap, a densely calcified mitral ring was noted.

CASE 9.—Mr. F. F. entered Stanford University Hospitals, at the age of 82, in 1942, because of inability to walk after a cerebral vascular injury; this promptly improved. There was no history of rheumatic fever or syphilis; several Wassermann tests of the blood gave negative results.

The arterial pressure was 240 mm. in systole and 80 mm. during diastole. The heart was slightly enlarged. There was a loud blowing aortic diastolic murmur and a soft systolic murmur along the left sternal border. There was no apical murmur. Pulmonary emphysema was marked.

An electrocardiogram showed sinus rhythm, P-R interval of 0.16 second, QRS duration of 0.08 second and left axis deviation with normal T waves. Roentgenograms revealed a wide tortuous calcified aorta, a prominent left ventricle and a calcification of the mitral annulus fibrosus.

CASE 10.—Mr. C. H., a granite cutter, was 68 when he entered the Stanford University Hospitals in 1936 because of intermittent indigestion for thirty years. He had never had rheumatic fever but had complained of a stiff neck and "sciatica" for many years. The heart was not enlarged, and the beats were regular at a rate of 60 per minute. There was a moderately loud, rough systolic murmur at the apex and the left sternal border, but it was loudest in the aortic area. Diastole was clear. There was no thrill, and the murmur did not reach the carotid arteries. Arterial pressure was 140 mm. during systole and 75 mm. in diastole. The radial arteries were thick and the branchial arteries tortuous. There were a few scattered rales. An electrocardiogram showed sinus rhythm, heart beat rate of 60 per minute, P-R interval of 0.18 second and QRS duration of 0.06 second. Roentgenologic study revealed pneumonoconiosis, duodenal ulcer and calcification of the mitral annulus fibrosus; the cardiac shadow was normal in size and shape. Indigestion was relieved by the usual methods. The patient returned in 1944 because of symptoms of disease in the urinary tract; physical observations of the heart were the same as before, and arterial pressure, electrocardiogram and roentgenographic appearance of the heart were all as they had been eight years earlier. Phonocardiograms revealed a few small presystolic vibrations; these were not made any more impressive, nor was a presystolic murmur heard, when the heart rate was slowed to 50 beats per minute and the P-R interval lengthened to 0.20 second by pressure on the carotid sinus after the administration of digitalis.

COMMENT

Ten patients with calcification of the mitral annulus fibrosus were observed during life; the diagnosis was made at necropsy for 1 and by roentgenologic means (confirmed twice at necropsy) for the others.

Sex and Age.—Seven of the 10 patients were women. In a much larger series [8] of similar patients there were also 2 women to every man;

in a thousand necropsies on cadavers divided equally by sex,[1d] calcification of the mitral annulus was found in 13.2 per cent of the women and 4.2 per cent of the men. The increased incidence of this disorder in women is particularly striking when the condition is contrasted with calcific aortic stenosis, for men with that disease greatly outnumber women.[9]

At the time of the first evidence of calcification the women were aged 58 to 82 (mean, 70) and the men 68 to 82 (mean, 73). Other investigators [10] have more evident data showing that the disorder affects men a few years later than it does women.

Pathologic and Etiologic Aspects.—Geerling,[1a] Giese [1b] and Ribbert,[1c] among other authors, have amply described the lesions with isolated calcification of the mitral annulus fibrosus; those found in our patients did not differ significantly from their descriptions. It should be noted that the mitral cusps may be thickened or even somewhat deformed near the annulus [8] in the absence of mitral stenosis or other convincing evidence of rheumatic heart disease.

Two patients (cases 5 and 8) had syphilis; nothing was seen in the necropsy of 1 to indicate that syphilis had anything to do with the calcification. Arterial hypertension was frequent but usually not severe; the diastolic pressure varied from 80 to 120 mm., even in the absence of heart block.

Scars of duodenal ulcer were found at necropsies in cases 3 and 5, while those in cases 8 and 10 were discovered by radiologists in the course of examinations made because of gastrointestinal symptoms with ulcer. We know of still another case, not reported in this paper, in which death resulted from a perforated duodenal ulcer. Yet the high incidence of duodenal ulcers in our cases may be largely accidental, owing to routine fluoroscopic examinations of the chests of patients about to ingest barium sulfate.

Many pathologists consider calcification of the mitral annulus to be a process similar to that of calcific aortic stenosis. Although the lesions at these two sites are otherwise similar, it is strange that at the mitral valve the cusps are usually spared and the annulus fibrosus involved while at the aortic valve the reverse is true. Neither Sosman [2a] nor Christian [11] has found isolated calcification of the supporting fibrous annulus of the aortic valve; Menezes de Oliveira [8] noted its rarity.

Yet the two lesions have much in common, and since recent writers [12] favor a rheumatic origin for calcific aortic stenosis it is possible that

9. McGinn, S., and White, P. D.: Clinical Observations on Aortic Stenosis, Am. J. M. Sc. **188**:1-15 (July) 1934.

10. Martens,[1d] Menezes de Oliveira.[8]

11. Osler,[8b] p. 1050.

12. Hall, E. M., and Ichioka, T.: Etiology of Calcified Nodular Aortic Stenosis, Am. J. Path. **16**:761-785 (Nov.) 1940.

calcification of the mitral annulus might also be rheumatic. None of our patients gave a history of rheumatic fever; none had auscultatory or roentgenologic signs of mitral stenosis (see following material), and in none of 3 cases was there evidence of rheumatic heart disease at necropsy. Gager and Pardee,[13] on the other hand, reported a case in which the pathologic observations were suggestive of rheumatic origin.

Menezes de Oliveira [3] indicated that the lesion was sometimes rheumatic; his criteria favoring this origin are: predominance on the valve leaflets, severe and multiple vavular lesions, vegetations, noncongenital fusion of valvular commissures and shortened thick chordae tendineae. Nonrheumatic calcification, on the other hand, is suggested by extensive calcification in the fibrous supporting rings (cardiac skeleton) with slight valvular lesions, or absence of such lesions and absence of other signs of endocarditis.[3] Of his 100 cases, 75 fell into the latter group, which he considered to be of arteriosclerotic origin.

Atherosclerosis of the aorta was prominent. Coronary atherosclerosis was severe in case 3 but relatively slight in cases 5 and 6. Pulmonary atherosclerosis was slight in case 3 but severe in case 6 in which fibrosis of the lungs was present. Unexpected lesions were the masses of calcium in the greatly thickened intima of the large arteries of the neck in case 3. Nearly occluding these vessels, the masses may have been related causally to the postural vertigo noted by the patient in this case and to her systolic thrill and murmur. Similar, but much less pronounced, calcification in early branches of the aorta were found in case 5. It seems likely that calcification of the mitral annulus is closely related to the degenerative vascular disturbances.

Blood counts were not remarkable in any case, and routine urinalysis showed only evidence of renal arteriosclerosis. The concentrations of various substances per hundred cubic centimeters of serum in cases 2, 6 and 7, respectively, were: calcium, 9.0, 11.3 and 9.5 mg.; inorganic phosphorus as phosphate, 3.1, 4.6 and 4.1 mg.; alkaline phosphatase activity, 6.4, 5.4 and 3.7 units; cholesterol, 285, 169 and 280 mg., and protein, 8.0, 7.9 and 7.5 Gm. These results are not striking but suggest a tendency toward increased concentrations of protein and, in 2 patients, of cholesterol.[14]

The lesions show no evidence of progression histologically; this is what might be expected if a single massive injury or other transient cause were followed by healing with fibrosis and calcification. This

13. Gager, L. T., and Pardee, H. E. B.: Intermittent Complete Heart-Block and Ventricular Standstill, Am. J. M. Sc. **169**:656-662 (May) 1925.

14. Kountz, W. B.; Sonnenberg, A.; Hofstatter, L., and Wolff, G.: Blood Cholesterol Levels in Elderly Patients, in Moore, R. A.: Ageing and Degenerative Diseases, in Biologica Symposia, Lancaster, Pa., Jaques Cattell Press, 1945, pp. 79-86.

view is supported by the benign clinical course observed in cases 7 and 10. On the other hand, calcification noted during October 1945 in case 4 was not seen, in spite of careful specific search fifteen months earlier; increasing calcification was observed in 1 patient over a nine year period.[15]

Heart Block.—Geerling's [1a] anatomic studies show that the portion of the mitral annulus fibrosus which lies in the interventricular septum is the least commonly calcified. Heart block may be expected when calcification extends into the septum, particularly when excrescences reach out from the ring to invade the conducting system more deeply; such localization may be as much a matter of chance as a question of degree of the lesion. Geerling [1a] and Ritchie [5] presented roentgenograms of two hearts taken after the deaths of patients in whom heart block had been present, and there was a prolonged conduction time in 1 of Saul's [16] patients, but apparently disturbances of conduction are rare.[3]

In at least 3 of the 4 cases with necropsy, reported by Comeau [17] as instances of paroxysmal complete heart block, calcification played a major part. Starling's patient with block, which was induced by swallowing and prevented by atropine, later was subject to permanent complete heart block, and at necropsy a calcareous lesion was described by T. Lewis.[18] With this background it is not surprising that of our 5 patients with complete heart block, sinus rhythm with normal conduction times reappeared temporarily in 2 (cases 1 and 5); the transient complete block in case 2 was probably related to digitalis.

We have not attempted to demonstrate the precise nature of the lesions located in the conducting system at necropsy, and it is quite possible that calcification was not the direct cause of block. In case 4, for example, calcification was not found for eight years after the discovery of complete heart block but was eventually seen after another year. As recently suggested,[19] transient ischemia of the nodal region might also be considered responsible for paroxysmal block.

The apical auricular murmur was never heard when auriculoventricular conduction was normal (see following material).

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15. Odqvist, H.: Studien über den Röntgenbefund bei intrakardialen, speziell perimitralen Verkalkungen, Acta radiol. **25**:686-700 (Nov.) 1944.

16. Saul, W.: Verdichtungen im Herzschatten, Fortschr. a. d. Geb. d. Röntgenstrahlen **46**:450-457 (Oct.) 1932.

17. Comeau, W. J.: Paroxysmal Complete Heart Block Alternating with Normal Rhythm and Conduction, Am. J. M. Sc. **194**:43-53 (July) 1937.

18. Lewis, T.: Postmortem Notes of Dr. J. H. Starling's Case of Heart-Block, Heart **9**:283-287 (Dec.) 1922.

19. Roos, A.: Paroxysmal Complete Heart Block, Produced by Ischemia of the Auriculoventricular Node, Am. Heart J. **30**:238-252 (Sept.) 1945.

Murmurs.—A loud, rough murmur accompanied ventricular systole in cases 1 to 3 and 5 to 7, was moderate in case 10 but was not prominent in cases 4, 8 and 9. It was usually most intense at the base and along the left sternal border from the second to the fifth interspace, but it was heard also at the apex in cases 1 to 6 and 10 and over the carotid artery in cases 1 and 3. There was an associated thrill in case 3 only.

Mitral regurgitation is a commonly given explanation for a systolic murmur confined to the apex but is hardly satisfactory when the apical murmur is even louder at the aortic area as in the present cases.[20] The left auricle was never found to be dilated (except with congestion and auricular fibrillation in case 2 and after a lapse of time in case 4), and it is difficult to imagine the dilatation of a valve ring which has first become heavily calcified. The heart as a whole was not enlarged in cases 7, 8 and 10, slightly enlarged in cases 1 (temporarily) 2 and 9 and moderately or greatly enlarged in cases 3, 4, 5 and 6; there was no more than a rough correlation, with several exceptions, between cardiac dilatation and the intensity of the systolic murmur. With no other apparent change the murmur first appeared in case 7 long after the calcific lesion was noted.

Although the second heart sound was normal in all patients, calcific aortic stenosis was sometimes suspected; it was not present in any of the necropsies. The masses of calcium found in the aortic branches in case 3 may have been the cause not only of the murmur but also of the thrill and attacks of postural dizziness noted in that patient. The degree of aortic or pulmonary atherosclerosis and dilatation may have been enough in all cases to account for the murmur with ventricular systole. The murmur of aortic insufficiency was heard in case 9.

Libman [7] has suspected the presence of calcification of the mitral ring on hearing a systolic murmur along the left sternal border but not in the aortic area; his description is applicable only in cases 7 and 8, so that the diagnostic value of such a murmur is not convincing. We have been unable to find a satisfactory case report describing the signs of mitral stenosis with calcification of the mitral annulus fibrosus. Cohen, Gray, Nash and Fink [21] wrote of a presystolic murmur in their case 2, but calcification was neither seen roentgenologically nor noted at necropsy. Menezes de Oliveira [8] found questionable diastolic murmurs in only 2 of 75 patients with "arteriosclerotic" calcification of the mitral annulus. In necropsies of 11 such patients, he found

20. Baker, L. A.; Sprague, H. B., and White, P. D.: The Clinical Significance of Loud Aortic and Apical Systolic Heart Murmurs Without Diastolic Murmurs, Am. J. M. Sc. **206**:31-43 (July) 1943.

21. Cohen, L.; Gray, I.; Nash, P. I., and Fink, H.: Calcareous Aortic Stenosis: Report of Nine Cases with Autopsy Findings, Ann. Int. Med. **13**: 2091-2103 (May) 1940.

slight mitral stenosis once and questionable mitral regurgitation once; otherwise there were no mitral abnormalities of functional importance and no left auricular dilatation.[22] In only 1 case did he judge the calcareous lesion to be the sole cause of a loud systolic murmur. In none of our patients with normal conduction time was there an apical murmur during ventricular diastole. On the other hand, a blowing murmur restricted to the apex during this part of the cardiac cycle was audible in the 4 ambulatory patients (cases 1 to 4) of the 5 with heart block. Records of the heart sounds not only confirmed the presence of an actual murmur, as distinguished from the auricular sounds which often accompany heart block, but showed it to be related to auricular activity. When this even took place early in ventricular diastole, the murmur was loudest; later it was less intense. These changes were easily detected on auscultation. As noted, the murmur was present in early diastole during a period of auricular fibrillation in cases 1 and 2; otherwise, the murmur never occurred during the period of rapid ventricular filling unless auricular activity coincided.

In some cases of heart block phonocardiograms have revealed prolonged sound vibrations associated with auricular activity,[23] but apparently these have not been interpreted as murmurs clinically. However, Wolferth and Margolies [24] and Stead and Kunkel [25] have reported on 2 patients (case 1 in each paper) with heart block and an auricular murmur appreciated as such on auscultation. We have phonocardiograms which confirm clinical observations that an apical murmur was present during ventricular diastole in 5 more elderly patients with conduction defects. Their cases are not reported in this paper because no calcification could be detected roentgenologically in spite of careful search, but it is of interest that case 4 was at first included with them.

Mechanisms which might be involved in the production of the auricular murmur will be discussed more completely elsewhere, but several points may be mentioned here. The murmur is not directly related to the calcareous lesion but does seem to be related to heart block; found in our patients only when block also occurred, it was absent even in them whenever the P-R interval happened to fall within the normal range, as in the first cycle of figure 2. Measurements of

22. These facts are not correctly cited in the book review.[8]

23. Orias, O., and Braun-Menéndez, E.: The Heart-Sounds in Normal and Pathological Conditions, London, Oxford University Press, 1939, p. 111.

24. Wolferth, C. C., and Margolies, A.: The Influence of Auricular Contraction on the First Heart Sound and the Radial Pulse, Arch. Int. Med. **46**:1048-1071 (Dec.) 1930.

25. Stead, E. A., Jr., and Kunkel, P.: Factors Influencing the Auricular Murmur and the Intensity of the First Heart Sound, Am. Heart J. **18**:261-270 (Sept.) 1939.

its time relationships further suggest that it does not occur with, but rather follows, auricular systole. Such behavior is quite unlike that of the presystolic murmur of rheumatic mitral stenosis, and there is neither pathologic nor roentgenologic evidence of obstruction to flow through the mitral orifice by calcification of its annulus fibrosus as a general rule.

Fibrosis of the mitral leaflets is a common occurrence in the aged; this, either alone or with the addition of calcification extending from the annulus fibrosus into the proximal portions of the cusps as in cases 3 and 5, need not obstruct the flow but might modify the usual movements of the leaflets which follow auricular systole. In the absence of conduction defects, no physical signs would appear. But with delayed ventricular systole, the thickened leaflets might conceivably permit reflux of blood into the auricle or might vibrate in the stream as ventricular filling continues; a murmur such as was found in our patients could be the result in either case.

Roentgenologic Aspects.—Several observers [26] have described the roentgenologic aspects of calcification of the mitral annulus fibrosus, differentiating this from the calcific lesions in the valve leaflets of patients with rheumatic mitral stenosis. Prominence of the left auricle is rarely found.

In a roentgenkymographic study, Sundberg [2c] calculated that six sevenths of the stroke volume is due to descent of the base of the heart toward the apex during systole. Roentgenkymograms in cases 2, 6, 7 and 9 all show this movement to be much more striking than the lateral motion of the walls (fig. 7), another bit of evidence confirming the opinion [27] that estimates of cardiac output based on roentgenkymography are not trustworthy.

Cardiac Symptoms.—Congestive heart failure occurred in 5 patients (cases 1, 2, 3, 5 and 6). Of these, heart block was present in all but the last. Congestion was not apparent in cases 4 and 7 to 10. Angina pectoris was surprisingly rare, occurring only in cases 2 and 3; myocardial infarction was found in the latter. Only 1 patient (case 5) had the Stokes-Adams syndrome. Cardiac symptoms seem to be even less common in cases reported by others; this is especially noteworthy when one recalls the age incidence of this disorder. We know of 1 other patient, not included in this report, in whom necropsy showed acute bacterial endocarditis as a complication.

With such a relative paucity of associated cardiac symptoms, it should not be surprising that in so many patients the calcific lesion is found by chance.

26. Footnote 2. Menezes de Oliveira.[8]

27. Hamilton, W. F.: Notes on the Development of the Physiology of Cardiac Output, Federation Proc. **4**:183-195 (June) 1945.

Prognosis.—Prognosis seems to be determined chiefly by the occurrence of heart block. Of the patients with block, those in cases 1, 2 and 3 died five, two and three years after the discovery of their lesions, and the one in case 5 died within a year of the onset of cardiac symptoms; the patient in case 4, on the other hand, is still living and ambulatory nine years after the onset of heart block. Without defective conduction the patient in case 6 died in six years but those in cases 7 to 10 are alive after one, three, eight and eleven years. The causes of death were cerebral vascular disease in case 1, myocardial infarction in case 3 and congestive heart failure in cases 2, 5 and 6.

It is most interesting that in case 7 the patient is alive and well as far as her heart is concerned, eleven years after the lesion was found. Likewise in case 10 the patient has no cardiac symptoms after eight years. The only apparent change in them was the development of a systolic murmur in the former; specifically, there was neither lengthening of conduction time nor change in the roentgenologic appearance. The clinical course in these cases suggests that calcification of the mitral ring is at the most a slowly progressive disorder after the initial damage has occurred.

Clinical Diagnosis.—After observing case 1, we ventured the diagnosis of calcification of the mitral annulus fibrosus in cases 2, 3 and 4 on finding complete heart block and an apical diastolic murmur in each of the elderly patients. The diagnoses were confirmed roentgenologically, even though digitalis played a part in the block in case 2 and only after a delay of three years in case 4.

On the other hand, the same diagnosis was not confirmed roentgenologically in 5 other elderly patients with identical cardiac signs. Whether calcification will eventually appear in them, as in case 4, is a question that must be left to the future; it is strongly suspected that noncalcific degenerative lesions are adequate to produce the syndrome.

SUMMARY

Clinical observations are recorded concerning 10 patients with calcification of the mitral annulus fibrosus.

The ages of the patients range from 58 to 82; 7 were women.

None had a history of rheumatic fever, and there was no convincing evidence of rheumatic heart disease in three necropsies. Atherosclerosis was marked; calcification of the large arteries to the neck was found at two of the necropsies.

Congestive heart failure occurred in 5 patients, angina pectoris in 2 only. Arterial hypertension was present in practically every case but was not often severe.

Five patients had complete heart block. This was paroxysmal in 2, while partial block in a third was temporarily made complete by digitalis. Four of these patients, but only 1 of those without block, have died.

In 7 patients there was a moderate or a loud, rough murmur with ventricular systole.

In the 4 ambulatory patients of the 5 with heart block there was a blowing apical murmur, related to auricular activity, during ventricular diastole; auricular sounds of uncertain nature were recorded for the fifth. This murmur did not occur in the patients with normal auriculoventricular conduction but it has been noted in other elderly patients with heart block and without roentgenologic evidence of calcification.

The significance of the murmurs is not clear, but they were not regarded as evidence either of mitral regurgitation or of mitral stenosis.

Two patients were observed again a decade after the discovery of their calcific lesions; no significant changes were found other than the appearance, in 1, of a systolic murmur. With regard to a third patient diligent roentgenologic study failed to demonstrate calcification eight years after the onset of complete heart block, but it was successful after one more year.

Calcification of the mitral annulus fibrosus may be suspected in elderly persons after the finding of heart block and an apical murmur associated with auricular activity during ventricular diastole.

ERYSIPELOTHRIX RHUSIOPATHIAE INFECTION IN MAN

Report of a Case with Cutaneous Bullae, in Which Cure Was Achieved with Penicillin

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THE numerous cases, which have been reported, of infection of human beings by Erysipelothrix rhusiopathiae, the causative agent of swine erysipelas, fall into three rather well defined clinical categories (see Klauder [1] for the literature). These are (1) a mild, localized cutaneous form (erysipeloid of Rosenbach [2]), (2) a severe, generalized cutaneous form and (3) a septicemic form, with or without cutaneous involvement, sometimes complicated by specific endocarditis (Russell and Lamb [3]). The less frequent clinical and anatomic manifestations which have been recorded are arthritis (Düttmann,[4] Brind [5] and Wüthrich [6]), meningitis (Dumont and Cotoni [7]), lymphangitis and lymphadenopathy (Schölzke [8]), optic neuritis (Peters [9]), intracranial abscess (Torkildsen [10]) and osseous necrosis (Klauder, Kramer and Nicholas [11]).

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From the Army Institute of Pathology, Army Medical Museum, Washington, D. C.

1. Klauder, J. V.: Erysipelothrix Rhusiopathiae Infection in Swine and in Human Beings, Arch. Dermat. & Syph. **50**:151-159 (Sept.) 1944.

2. Rosenbach: Ueber das Erysipeloid, Arch. f. klin. Chir. **36**:346-350, 1887.

3. Russell, W. O., and Lamb, M. E.: Erysipelothrix Endocarditis, J.A.M.A. **114**:1045-1050 (March 23) 1940.

4. Düttmann, G.: Schweinerotlauf und Erysipeloid, Beitr. z. klin. Chir. **123**: 461-470, 1921.

5. Brind, A. I.: Arthritis of Erysipeloid Etiology, Novy khir. arkhiv. **47**: 177-181, 1940.

6. Wüthrich, A.: Die chronische Erysipeloidarthritis mit röntgenologisch sichtbaren Knochenzerstörungsvorgängen, Beitr. z. klin. Chir. **174**:98-103, 1942.

7. Dumont, J., and Cotoni, L.: Bacille semblable au bacille du rouget du porc rencontré dans le liquide céphalo-rachidien d'un méningitique, Ann. Inst. Pasteur. **35**:625-633, 1921.

8. Schölzke, K. H.: Seltener klinischer Verlauf eines Erysipeloids, Med. Klin. **33**:1299-1300, 1937.

9. Peters: Personal communication; cited by Callomon.[12]

10. Torkildsen, A.: Intracranial Erysipeloid (Swine-Erysipelas) Abscess: A Variety of Abscess Not Hitherto Observed, Bull. Hyg. **18**:1013, 1943; abstracted, Acta chir. Scandinav. **89**:89-96, 1943.

11. Klauder, J. V.; Kramer, D. W., and Nicholas, L.: Erysipelothrix Rhusiopathiae Septicemia: Diagnosis and Treatment, J. A. M. A. **122**:938-943 (July 31) 1943.

Characteristically, the cutaneous lesions assume the form of superficial, more or less circumscribed, slightly elevated and moderately edematous areas of erythema (Callomon [12]). Vesication of the eruption has been but rarely observed and then chiefly in the form of hemorrhagic blebs at the site of inoculation (Klauder [1]). In the case reported in this paper bullous vesication was an outstanding feature and engendered considerable diagnostic difficulty and therapeutic delay because it has not heretofore been recognized that erysipelothrix infection in man may assume this form.

Intensive therapy with penicillin was instituted because of the results reported by Heilman and Herrell,[13] who found this antibiotic substance highly potent in the treatment of experimental infection of mice. The rapid and complete clinical cure which resulted indicates that penicillin therapy is more effective in the treatment of this disease than the use of specific antiserum or of sulfonamide compounds (Klauder and Rule [14]), cryotherapy (Griswold and Bowen [15]) or ultraviolet irradiation (Mühlpfordt [16]).

REPORT OF CASE

J. A. H., a 46 year old white farmer, was admitted to the Eugene Leland Memorial Hospital, Riverdale, Md., on Jan. 20, 1945 (service of Dr. Wendell E. Malin, Riverdale, Md.). Four days before admission he had slaughtered and dressed a "sick" hog. The following day he noticed a red, swollen, tender area on his right hand in the vicinity of an abrasion which had been present before the slaughter. The redness and swelling extended rapidly and by the next day had reached the elbow. Numerous vesicles formed, and there was intense itching of the involved skin; the patient and his family physician thought that he had "poison ivy." Sulfonamide compounds were administered, and wet dressings were applied, without benefit. On the fourth day lesions appeared on the neck, the face, the ears (fig. 1) and the left hand (fig. 4 *C*); there was stiffness as well as pain in the right shoulder, and the patient felt feverish and ill. By the time he entered the hospital that evening large bullae were present on the hands and the right arm; areas of redness were present on the face and the neck, and the eyes were closed by edema of the eyelids (fig. 1). The patient had lapsed into stupor.

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12. Callomon, F.: Pseudoerysipel, Erysipeloid, in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1929, vol. 9, pt. 1, pp. 93-124.

13. Heilman, F. R., and Herrell, W. E.: Penicillin in Treatment of Experimental Infections Due to Erysipelothrix Rhusiopathiae, Proc. Staff Meet., Mayo Clin. **19**:340-345, 1944.

14. Klauder, J. V., and Rule, A. M.: Sulfonamide Compounds in Treatment of Erysipelothrix Rhusiopathiae Infections, Arch. Dermat. & Syph. **49**:27-32 (Jan.) 1944.

15. Griswold, C. M., and Bowen, S. S.: Treatment of Erysipeloid by Cryotherapy, Arch. Dermat. & Syph. **49**:348-350 (May) 1944.

16. Mühlpfordt, H.: Rotlaufserumbehandlung oder Höhensonnenintensivbestrahlung des Erysipeloids? Dermat. Ztschr. **60**:445-450, 1931.

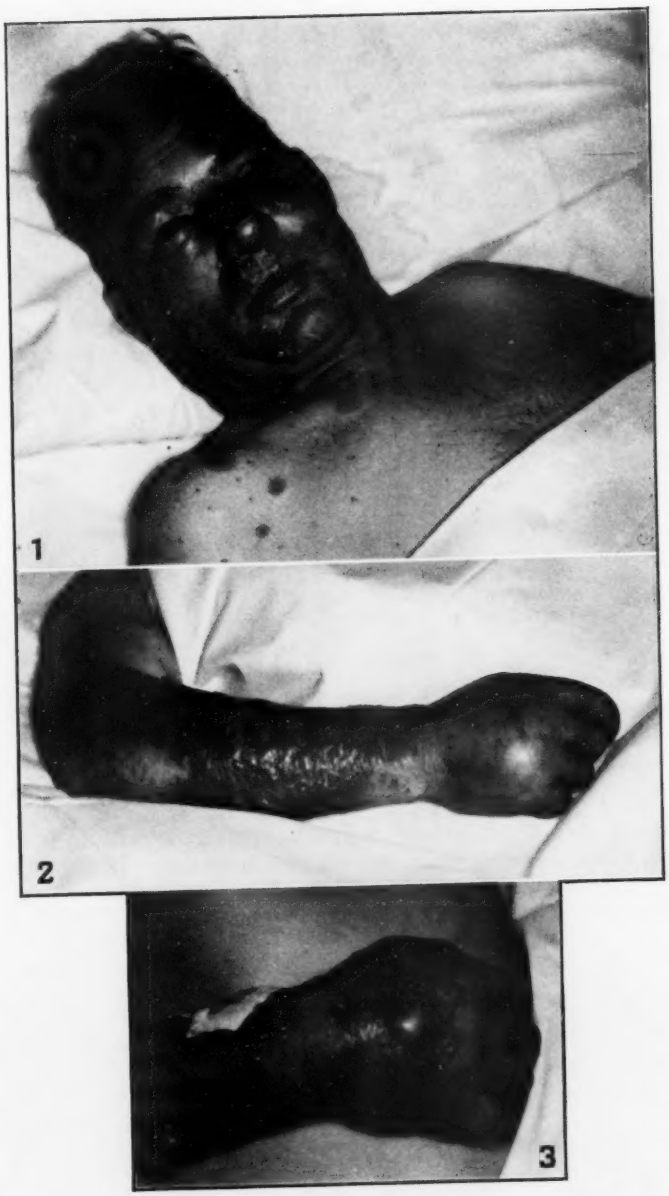

Fig. 1.—Erysipelothrix rhusiopathiae infection in a 46 year old white man.

Additional information, which proved to be of considerable importance, was elicited later. It was learned that three weeks prior to the onset of the present episode he had had several painful reddish lesions on his right hand. These had healed slowly and had almost disappeared at the time he slaughtered the hog, four days before his admission to the hospital.

Examination.—When the patient was admitted to the hospital, his temperature was 98.4 F.; the respirations were 20 and the pulse beats 80 per minute and the blood pressure was 180 systolic and 90 diastolic. The significant features on physical examination were limited to the skin. Eruptions were present on both of the upper extremities, the face, the ears, the neck, the shoulders and the sternum; the changes were most extensive on the right hand and forearm. A traumatic abrasion, about 1 cm. in diameter, on the dorsum of the right hand was apparently the site of inoculation; it was covered with a black crust and surrounded by a wide zone of intense redness and edema. The right hand and forearm were studded with huge bullae, which appeared, in areas, to have coalesced. The surface was tense, shiny and bluish purple, and the contents were clear. The intervening skin was diffusely erythematous, and there was no sharp transition to normal integument. A few bullae were present on the left

Fig. 2.—Appearance of right hand and arm fourteen days after the patient's admission to the hospital. They show exfoliation of large sheets of tissue.

hand and forearm (fig. 4 *C*). The lesions on the face, the neck and the shoulders were of an entirely different character; they were sharply circumscribed, slightly raised and indurated plaques (fig. 1), which were bright red at the periphery and purplish in the center. Ill defined areas of erythema were observed on the chest and the back at this time, but there were no discrete lesions.

Laboratory Data.—During the first week, blood counts revealed 12,000 to 15,000 leukocytes per cubic millimeter, with 85 per cent polymorphonuclear leukocytes. On one occasion, 4 per cent eosinophils was reported; otherwise, the differential count was normal. Several urinalyses disclosed no significant abnormalities. On January 20 examination showed 6.1 mg. of the sulfonamide compound per hundred cubic centimeters of blood; on January 26 the total chlorides were 570 mg.

A direct smear of the contents of a bleb revealed a few gram-positive cocci, resembling staphylococci. Cultures on plain broth, Loeffler's agar and blood agar yielded Staphylococcus (type not stated), which was thought to be a contaminant. Culture of blood taken on the day after the patient's admission to the hospital was negative for staphylococci, but the procedure was not carried

out under optimal conditions. Culture of a second sample, obtained after penicillin therapy was well under way, and of a fragment of exfoliated skin, was also negative for staphylococci.

The Wassermann test of the blood and agglutination tests for typhoid, paratyphoid, undulant fever and tularemia were negative. Two samples of serum, obtained on the fifth and fourteenth days after the patient's admission to the hospital, were submitted for agglutination tests for Erysipelothrix to the Pathological Division of the Bureau of Animal Industry, United States Department of Agriculture. The report read in part: "Agglutination tests were conducted on the two samples of serum. The first reacted at 1:200 dilution with swine erysipelas tube antigen and very rapidly with the plate antigen. The second sample of serum failed to agglutinate plate antigen when it was tested in the usual manner. On dilution of the serum with saline solution, a fine clumping of the plate antigen was noted. This second sample of serum agglutinated tube antigen at 1:25 did not react at 1:50 and 1:100 but reacted strongly at 1:250 and 1:1,000." Agglutination tests on a third sample of serum, taken three weeks after the patient was discharged from the hospital, gave negative results.

The Pathological Division of the Bureau of Animal Industry of the United States Department of Agriculture and the Maryland Livestock Sanitary Board were instrumental in recovering for study a portion of the carcass of the hog which had been slaughtered by the patient. Typical rhomboid cutaneous lesions were present, and agglutinations were positive for swine erysipelas. Ery. rhusiopathiae grew on culture of the skin and of material from the joints of the hog. Additional members of the herd to which this hog belonged were found to be infected.

Course.—Penicillin therapy was initiated at the time of the patient's admission to the hospital at an arbitrary dose of 20,000 units, administered intramuscularly every three hours. This appeared to bring about slight improvement and to arrest the fulminant progress of the disease, but when the diagnosis was definitely established the quantity was increased to 40,000 units every three hours. Twenty-four hours later the patient emerged from his stupor. During the succeeding days there was a dramatic clinical improvement. The temperature, which had fluctuated between 102 and 104 F., and the pulse rate, which had ranged between 100 and 130, rapidly returned to normal. About fifteen days after his admission to the hospital it was necessary to interrupt the administration of penicillin; fever and constitutional symptoms recurred but cleared promptly when therapy was resumed.

The erythema of the upper extremities spread rapidly to the shoulders, the neck and the face. By the end of the first week these regions had become intensely violaceous, in striking contrast to the uninvolved areas (fig. 3 *A*). During the first few days large irregular erythematous discolorations developed on the back (fig. 3 *B*). The erythema remained after regression and exfoliation of the bullae and plaques were complete; a significant flush on the face and the upper extremities persisted for several weeks after the patient was discharged.

The bullous lesions of the hands and the arms progressively enlarged, sometimes by coalescence, and after they remained stationary in size for a varying period their fluid contents were absorbed. None of the lesions suppurated. The thick layers of dried, loosened skin which remained were ultimately desquamated (figs. 2 and 4, *D* and *E*). Some of the exfoliated tissue came off in large sheets, and that over the hands could be pulled off like parts of a glove. These changes

Fig. 3.—*A*, appearance of the patient fourteen days after his admission to the hospital. He has recovered from his stupor. There is marked reduction in the edema of the face and neck. Note the deep erythema of the arms, the shoulders, the neck and the face and the crops of fresh lesions on the chest. *B*, appearance of the patient's back fourteen days after his admission to the hospital. There are older confluent and recent discrete lesions on the back with patchy scaling.

Fig. 4.—*A*, eruptions fourteen days after the patient's admission to the hospital. There are circumscribed erythematous plaques on the legs reminiscent of "diamond skin" lesions in swine. *B*, fresh crop of lesions on the chest fourteen days after the patient's admission to the hospital. They consist of red papules occurring in groups. *C*, *D* and *E*, the left hand on the fifth, the fourteenth and the thirty-first day, respectively. The huge bleb in *C* is dried and loosened in *D* and almost completely desquamated in *E*.

recalled the extensive sloughing which sometimes occurs in the hog (Stiles and Davis [17]).

The flat circumscribed lesions present on the neck and the shoulders at the time of the patient's admission to the hospital continued to appear in crops on the chest (fig. 4 *B*), in the axillas and on the abdomen and the legs. They began as clusters of papules which coalesced to form circumscribed plaques. On the legs, their appearance was somewhat reminiscent of the so-called "diamond skin" or "urticarial" patches of the hog (fig. 4 *A*). Lesions of this type never vesicated. They turned purple, and the color faded from the center outward; these changes were associated with a moderate degree of scaling in striking contrast to the exfoliation of thick layers of tissue in the areas of vesication.

The evolution of the cutaneous lesions was accelerated, and the edema of the face and the neck, which had profoundly altered the patient's appearance,

Fig. 5.—General appearance of the patient thirty-one days after his admission to the hospital.

receded rapidly after the dose of penicillin was increased (fig. 5). The patient was discharged from the hospital six weeks after his admission, completely recovered. At present, ten months after his illness, he shows no evidence of chronic infection or complications.

Histologic Observations.—The first specimen was taken from a bleb on the left hand three days after the patient's admission to the hospital (fig. 6, *A* and *B*). It was evident that the vesication had occurred in the stratum germinativum of the epidermis. Intracellular and intercellular edema involved groups of cells in this layer in areas where cavitation had not as yet occurred. Small vesicles,

17. Stiles, G. W., and Davis, C. L.: Swine Erysipelas and Its Economic Importance, J. Am. Vet. M. A. **84**:895-906, 1934.

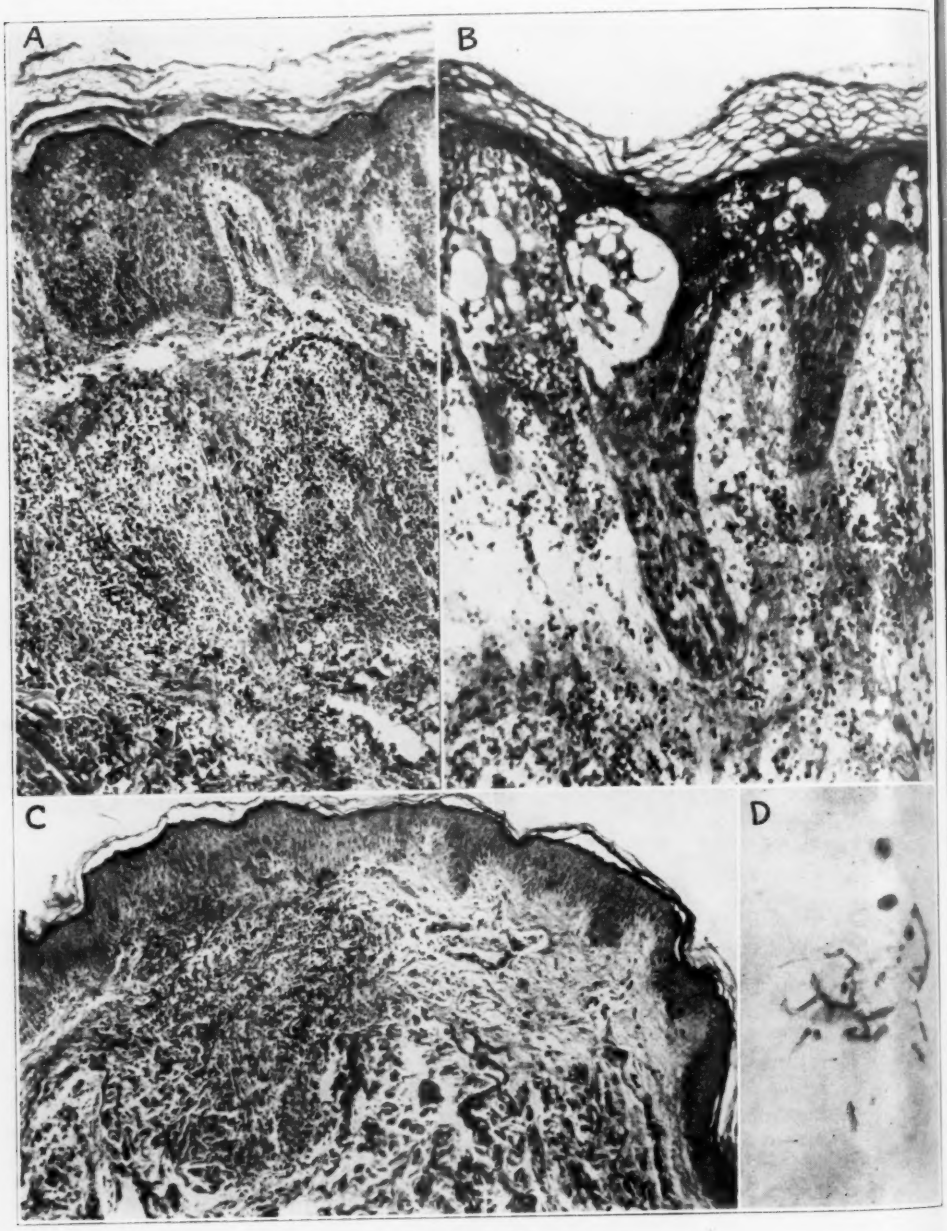

Figure 6

(See legends on opposite page)

whose diameters corresponded to those of two or three prickle cells, were numerous and sometimes occurred in groups which had partially fused (fig. 6 *B*). The largest cavities, which had evidently formed by coalescence, were covered with a few layers of cells belonging to the stratum germinativum, the stratum granulosum and the stratum corneum. On the side of the dermis there remained a thinned-out layer of basal cells which in some areas was broken through, allowing the bleb to communicate with the edematous papillary layer of the cutis. In some areas the surface layers of cells were necrotic. In one section, balloon degeneration of prickle cells and cavitation by reticular colliquation were evident.

The bullae contained serum, fibrin, erythrocytes, polymorphonuclear leukocytes, epithelial cells in various stages of degeneration and nuclear debris. Similar constituents were present in some of the smaller vesicles. Occasionally, dense collections of polymorphonuclear leukocytes gave the impression of early formation of pustules. In one section a few of these were located just beneath the stratum lucidum.

The epidermal pegs were elongated and in some areas were separated by edematous and clubbed papillae of the dermis. Numerous polymorphonuclear leukocytes were marginated along the dermatoepidermal junction; some of the pegs were invaded by these cells as well as by occasional lymphocytes. A severe degree of serohemorrhagic edema was present in the papillary zone of the cutis. In this region the capillaries were extremely dilated and engorged with erythrocytes. Interfibrillar accumulations of serum and fibrin and areas of hemorrhage were present. The dermal collagen was swollen, and there was some loss of fibrillar markings. The lymph vessels were moderately dilated and appeared empty. Cellular infiltration of this region was relatively slight and consisted of scattered polymorphonuclear leukocytes and occasional eosinophils. Elastic fibers stained poorly and appeared frayed out.

The infiltrate was concentrated just below the papillary layer of the cutis and was composed of polymorphonuclear leukocytes and eosinophils. In some areas, nodular collections of polymorphonuclear leukocytes were so dense as to suggest early abscess formation. The blood vessels in this layer were filled with polymorphonuclear leukocytes; here, too, the collagenic fibers were noticeably swollen. The inflammation extended, particularly around the blood vessels and the sweat glands, through the cutis to its junction with the panniculus. At the edge of the lesion, there was a gradual transition to normal skin.

EXPLANATION OF PLATE.

Fig. 6.—*A*, low power view of the epidermis and the upper part of the cutis in the first specimen. Note the intercellular and intracellular edema in the stratum germinativum, the severe edema and the capillary engorgement in the papillary layer of the cutis and the infiltrate concentrated in the subpapillary layer and the zona reticularis. × 100. *B*, higher power view of first specimen. The epidermis shows various stages of vesication. Note the smaller cavities to the right and the large cavity to the left, which has ruptured through the basal layer into the edematous dermis. Serum, fibrin, degenerated epithelial cells and polymorphonuclear leukocytes may be seen in the spaces. Note the intercellular edema in the pegs, the edema and clubbing of the papillae and the severe edema and hemorrhage in the cutis. × 200. *C*, low power view of second specimen. Note the widening of the epidermis, the moderate perivascular collections of lymphocytes and the wedge-shaped dense infiltrate reaching to the epidermis. × 100. *D*, detail of the second specimen. A group of Ery. rhusiopathiae is seen in the center of the lesion illustrated in *C*. × 2,700.

No bacteria were found in sections stained by the Giemsa, Warthin-Starry, Ziehl-Neelsen and Brown and Brenn methods. Mast cells were not significantly increased.

The second specimen was excised on the eighteenth day of illness from a flat plaque on the chest. The histologic changes were less severe than those in the previous sections (fig. 6 *C*). The epidermis was widened and lightly infiltrated by polymorphonuclear leukocytes and lymphocytes. Intracellular and intercellular edema was present but to a lesser degree than in the first specimen. There was no histologic evidence of vesicle formation.

Moderate numbers of lymphocytes were distributed around the blood vessels of the subpapillary layer of the cutis. In addition, a wedge-shaped and rather sharply delimited collection of polymorphonuclear leukocytes was present. It extended from the middle of the cutis to the basal layer of the epidermis and suggested an early focus of suppuration, possibly of embolic origin. Stains for bacteria revealed a cluster of gram-positive organisms with the characteristic appearance of Ery. rhusiopathiae in the center of this lesion (fig. 6 *D*).

COMMENT

The diagnosis of erysipelothrix infection was established by the rising titers of agglutinins in the patient's serum and by the presence of characteristic bacteria in sections of a cutaneous lesion. Although efforts to recover the organisms from samples of blood and fragments of exfoliated skin failed, cultures of the skin and of material taken from the joints of the hog responsible for the infection yielded Ery. rhusiopathiae. It appears likely that at one time infection of the blood stream existed, since widespread dissemination of the eruption in this disease is often associated with sepsis and the histologic characteristics of one lesion suggested an embolic origin.

The bullous character of the eruption which distinguished the early stage is decidedly unusual (Callomon [12] and Nékám [18]). In the literature the scattered references to vesiculation allude chiefly to the formation of hemorrhagic blebs at the site of inoculation (Klauder [1]), although in a few instances formation of vesicles has been observed in man (Düttmann,[4] Veilchenblau,[19] Arnholz [20] and Sieben [21]) and in swine (Hutyra, Marek and Manninger [22]).

18. Nékám, L.: Corpus Iconum Morborum Cutaneorum, Leipzig, Johann Ambrosius Barth, 1938, vol. 5, pt. 3, pp. 4402 and 4410.

19. Veilchenblau, L.: Zur Uebertragung des Schweinerotlaufs auf den Menschen, Deutsche med. Wchnschr. **47**:1030-1031, 1921.

20. Arnholz, F.: Zur Pathologie und Therapie des Erysipeloids, Arch. f. klin. Chir. **135**:736-750, 1925.

21. Sieben, H.: Generalisierter Schweinerotlauf beim Menschen, Med. Klin. **21**:129-130, 1925.

22. Hutyra, F.; Marek, J., and Manninger, R.: Special Pathology and Therapeutics of the Diseases of Domestic Animals, Chicago, Alexander Eger, 1938, vol. 1, p. 84.

The bullae produced a picture reminiscent of pemphigus vulgaris (Nékám,[18] illustration no. 2796) and dermatitis venenata. The intense pruritus associated with the blebs, their rapid spread, the infiltrate with numerous eosinophils, the capillary engorgement and the swelling of collagen suggest that hyperergy may have played a role in the exceptional course which the infection pursued.

The importance of the imperfectly understood allergic phenomena in erysipelothrix infection has been recognized by many observers (Callomon[12]). Belgodere[23] suggested that "erysipeloid may perhaps appear only in those persons who, by reason of their profession, have already been subjected to previous contacts, as a result of which they have become sensitized." Accidents ascribable to anaphylaxis are frequent during vaccination of animals (Monnier[24]). Curious immediate and delayed reactions in the vicinity of the site of an injection of immune serum have been observed (Callomon[12]).

Precipitins (Ascoli[25]) and agglutinins (Schoening, Creech and Grey[26]) have been described. Jadassohn and Mu[27] referred to a bacterial product, erysipeloidin, which retains some of the antigenic properties of the whole organism. In the case reported in this paper and in the cases reported by Schoening and Creech[28] and Ingram and Stuart[29] the titer of agglutinins reached 1 to 1,000 at the height of the illness and returned to 0 several weeks after recovery. Bierbaum and Gottron[30] reported normal titers of agglutinins in cases of the mild, localized form. Erysipelothrix infection does not confer lasting immunity; infection may readily occur again (Biberstein[31]).

23. Belgodere, G.: Supplément à l'histoire de l'érysipéloide (inoculation à l'homme du bacille du rouget du porc), Ann. de dermat. et syph. **6**:193-228, 1935.

24. Monnier, J. C. E. H.: Le rouget humain, Thesis, Paris, 1935, pp. 1-110.

25. Ascoli, A.: Die Thermopräzipitinreaktion als allgemeine serodiagnostische Methode: Ihre Anwendung bei der Diagnose des Schweinerotlaufs, Berl. tierärztl. Wchnschr. **28**:165-167, 1912.

26. Schoening, H. W.; Creech, G. T., and Grey, C. G.: A Laboratory Tube Test and Whole-Blood Rapid Agglutination Test for the Diagnosis of Swine Erysipelas, North Am. Vet. **13**:19-25, 1932.

27. Jadassohn, W., and Mu, J. W.: Ueber die Immunbiologie der Haut beim Rotlauf (Erysipeloid), Arch. f. Dermat. u. Syph. **162**:210-216, 1930.

28. Schoening, H. W., and Creech, G. T.: Serological Studies of Swine Erysipelas with Particular Reference to Agglutination, J. Agric. Research **50**:71-79, 1935.

29. Ingram, J. T., and Stuart, R. D.: Erysipeloid, Brit. J. Dermat. **46**:303-308, 1934.

30. Bierbaum, K., and Gottron, H.: Zur Kenntnis des Erysipeloids Rosenbach unter besonderer Berücksichtigung seiner Beziehungen zum Schweinerotlauf, Dermat. Ztschr. **57**:5-27, 1929.

31. Biberstein, H.: Untersuchungen über Hautreaktionen bei menschlichen und tierischem Rotlauf, Arch. f. Dermat. u. Syph. **168**:146-160, 1933.

Jadassohn and Mu [27] infected and reinfected rabbits by the intracutaneous route. The lesions produced were more localized, indurated and nodular, and the erythema was smaller in area, when the animal had been previously inoculated. Biberstein [31] found that 88 per cent of patients with active infections reacted to the intracutaneous injection of fresh erysipelothrix vaccine or even old filtrates of killed cultures (erysipeloidin).

The group of hogs with erysipelothrix infection which Nieberle [32] described had previously been vaccinated with a combination of immune serum and virulent erysipelothrix. A characteristic form of cutaneous necrosis and sloughing occurred, which showed, in sections, swelling of the dermal collagen, degeneration of fibroblasts, hyaline thrombosis of dilated capillaries and arterioles and hyalinization of the walls of blood vessels. Nieberle saw a similarity between these alterations, which he interpreted as expressions of hyperergy, and those of the Arthus phenomenon and suggested that there may occur a reaction in the skin between the antigen produced in the current infection and the immune bodies resulting from the prior vaccination.

Further studies are required to clarify the states of altered reactivity which may be induced by an initial erysipelothrix infection. From the available evidence it seems likely that in the case reported in this paper a prior episode of the disease, the clinical form of which was that of erysipeloid of Rosenbach, existed during the three weeks before the patient's admission to the hospital and induced a hyperergic state which influenced the reaction to subsequent reinfection.

Several differential counts revealed an increase of polymorphonuclear leukocytes but not of monocytes. Egehøj [33] has reported monocytosis in swine, and Klauder [1] in man.

According to Gans,[34] the histology of the cutaneous lesions is not well known. His description, like those of Delbanco,[35] Bazzoli [36] and Callomon,[12] stresses the relative absence of changes in the epidermis and the presence of serous inflammation, especially of the corium, with widening of lymph spaces and dense perivascular infiltration of lymphocytes and mast cells. The changes in the epidermis reported by Cheval-

32. Nieberle, K.: Ueber hyperergische Hautentzündung beim Schwein, Verhandl. d. deutsch. path. Gesellsch. **26**:239-243, 1931.

33. Egehøj, J.: Similarity of Blood Picture in Erysipelas of Swine and Infectious Mononucleosis of Man, Ugesk. f. læger **99**:698-699, 1937.

34. Gans, O.: Histologie der Hautkrankheiten, Berlin, Julius Springer, 1925, vol. 1, pp. 335-336.

35. Delbanco, E.: Ueber das Erysipeloid, Deutsche Med.-Ztg. **19**:781-784, 1898.

36. Bazzoli, L.: Il mal rossino e l'eresipeloide, Arch. ital. di dermat., sif. **2**: 449-472, 1927.

lier and associates,[37] namely, edema, leukocytic infiltration and necrosis of the islands of cells in the malpighian layer progressing to the formation of vesicles, parallel closely those observed in the first specimen in the present case.

Relatively few histologic reports on cutaneous lesions in swine have been recorded. In a recent report (Weidman, in Klauder [1]) the description underlines the fact that the cleaning and dehairing technics to which slaughtered hogs are subjected in the packing houses result in the loss of the epidermis and often of the upper portion of the cutis and render the material unsuitable for study.

Penicillin administered intramuscularly in a dose of 20,000 units every three hours for several days brought about moderate improvement; doubling the dose resulted in a dramatic clinical recovery. In all, the patient received 8,000,000 units during twenty days.

SUMMARY

An erysipelothrix infection of a human being, who acquired it by direct contact with a hog suffering from swine erysipelas, was distinguished clinically by the extremely rapid dissemination of the eruption, the severe pruritus and the development of huge bullae. These features and the histologic observations, particularly the swelling of the collagen, the numerous eosinophils in the infiltrate, the capillary engorgement and the serohemorrhagic edema of the dermis, indicate that the unusual manifestations of the disease may have had an allergic basis. A previous erysipelothrix infection of localized character probably induced the hyperergic state.

Intensive treatment with penicillin effected a complete recovery.

37. Chevallier, P.; Colin, P.; Levy-Bruhl, M.; Ely, L., and Moricard, R.: Fin de l'observation de rouget du porc generalisé chez l'homme, Bull. Soc. franç. de dermat. et syph. **39**:106-112, 1932.

ACTINOMYCOSIS DUE TO NOCARDIA ASTEROIDES

Report of Two Cases

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SINCE aerobic types of Actinomyces may be highly pathogenic to man and are not so well known as the anaerobic Actinomyces bovis, the death of 2 patients infected with an aerobic variety appears worthy of record, not only because of the rarity of the organism, but also to emphasize the necessity of accurate diagnosis and vigorous therapy.

In 1891, Eppinger [1] reported the finding of an aerobic gram-positive, acid-fast actinomyces in cerebral abscesses and meningeal exudate of a man who became delirious and died in two weeks. This organism readily grew on ordinary mediums as small starlike colonies, due to the radiating filaments, and was named Cladothrix asteroides. It has since been known as Streptothrix eppingeri, Streptothrix asteroides, Oospora asteroides and Actinomyces asteroides, and is now called Nocardia asteroides.[2]

In 1921, Henrici and Gardner [3] were able to collect but 26 reported cases of infections with aerobic acid-fast Actinomyces, and the causative organisms fell into three different types, which differed chiefly in the color of the growth on solid medium and in other minor biologic characters. All but 3 of these 26 cases were apparently of pulmonary origin, and all but 1 were fatal. Henrici and Gardner also reported a fourth type, which they isolated from the sputum of a 31 year old woman with a cough of three years' duration. It differed slightly from the three types

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1. Eppinger, H. L.: Ueber eine neue, pathogene Cladothrix und eine durch sie hervorgerufene Pseudotuberculosis, Beitr. z. path. Anat. u. z. allg. Path. **9**:287, 1891.

2. (*a*) Drake, C. H., and Henrici, A. T.: Nocardia Asteroides, Am. Rev. Tuberc. **48**:184, 1943. (*b*) Waksman, S. A., and Henrici, A. T.: The Nomenclature and Classification of the Actinomycetes, J. Bact. **46**:337, 1943.

3. Henrici, A. T., and Gardner, E. L.: The Acid-Fast Actinomyces, with a Report of a Case from Which a New Species Was Isolated, J. Infect. Dis. **28**:232, 1921.

previously described, and because of the chalky white appearance of the growth, was named Nocardia gypsoides. Later, Henrici [4] reported that after repeated subcultures the strain had become almost identical with N. asteroides. Baldacci [5] proposed reducing N. gypsoides and the related strains of aerobic acid-fast Actinomyces with only minor differences in their biologic characters to the rank of variants of N. asteroides.

In 1937, Goldsworthy [6] reported a fatal case of pulmonary actinomycosis in a man of 69 years from whose sputum a variant N. asteroides had been isolated.

Kessel and Goolden,[7] in 1938, in comparing eleven strains of Actinomyces recovered from human lesions, included 1 case in which cultures taken from the lungs, and the meninges at autopsy yielded an aerobic organism dispersed in branching filaments that did not produce granules and which seemed identical with N. asteroides 323 from the American Type Culture Collection.

Benbow, Smith and Grimson [8] in 1944, reported 2 cases of N. asteroides infection with pulmonary and multiple subcutaneous abscesses and sinuses, with a cerebral abscess suspected in 1. The organisms were isolated from the sputum and subcutaneous lesions of both. Treated by bed rest, surgical drainage, vitamins, sulfonamide drugs, iodides and roentgen therapy, both patients made slow but steady improvement and apparently were well after a year.

In 1945, Binford and Lane [9] isolated N. asteroides from a chronic suppurative pneumonitis, massive cerebral abscess and ischiorectal abscess found at necropsy in a man aged 51 under observation for a suspected tumor of the brain.

It is noteworthy that 28 of the 32 persons reported infected with N. asteroides were dead at the time the reports were published. In 20 of the cases diagnosis was made only at necropsy, and the organism was demonstrated in 12 during life but usually in the terminal stage of the disease. Twenty-eight cases were of pulmonary infection, and the brain was the site of metastases in at least 10. Of the 4 patients who

4. Henrici, A. T.: Molds, Yeasts and Actinomycetes, New York, John Wiley & Sons, Inc., 1930, p. 249.

5. Baldacci, E.: Revisione di alcune specie del G. Actinomyces, Mycopathologia **1**:68, 1938.

6. Goldsworthy, N. E.: Pulmonary Actinomycosis Caused by an Acid-Fast Species of Actinomyces, J. Path. & Bact. **45**:17, 1937.

7. Kessel, J. F., and Goolden, E. B.: Comparison of Strains of Actinomyces Recovered from Human Lesions, Am. J. Trop. Med. **18**:689, 1938.

8. Benbow, E. P., Jr.; Smith, D. T., and Grimson, K. S.: Sulfonamide Therapy in Actinomycosis: Two Cases Caused by Aerobic Partially Acid-Fast Actinomyces, Am. Rev. Tuberc. **49**:395, 1944.

9. Binford, C. H., and Lane, J. D.: Actinomycosis Due to Nocardia Asteroides, Am. J. Clin. Path. **15**:17, 1945.

survived, 1 was cured by amputation of the infected foot; another [3] was treated with an antigen made from the cultures, but after a year it appeared that the disease had progressed so that the patient had cough, sputum, pulmonary hemorrhages, pain referable to the chest and loss of weight, and the final outcome is not known; the other 2 were apparently cured of infections of the lungs and the chest wall by surgical drainage, sulfonamide compounds, iodides and roentgen therapy. It seems probable that if an early diagnosis were established and adequate therapy instituted the mortality rate might be considerably reduced.

Two cases of infection with aerobic Actinomyces will be reported.

REPORTS OF CASES

CASE 1.—A white retired banker of 63 entered Stanford Hospital on Feb. 27, 1943, because of cough and fever for about six weeks. The family and past history were not contributory, except that he had had mild diabetes mellitus for fifteen years, well controlled by small doses of regular insulin. He lived in a small town in central California, had not been in the San Joaquin Valley for years, and had no known contact with parrots, poultry, livestock or persons with pulmonary disease.

The present illness began in January with a hacking cough, dry at first, but later productive of about a cupful of thick, foul, yellow-green, occasionally blood-tinged sputum daily. General malaise, night sweats, fever and anorexia appeared, and he lost 40 pounds (18.1 Kg.) in weight. A diagnosis of bronchitis was made by his local physician, and he was treated with sulfadiazine for a few days without improvement. He was referred to Stanford Hospital.

Physical Examination.—The temperature was 38.5 C. (101.3 F.), the pulse rate 100, the respiration rate 24, the blood pressure 138 systolic and 80 diastolic and the weight 65.9 Kg. (145 pounds). He was thin, appeared acutely ill and coughed frequently, bringing up large amounts of foul, greenish yellow sputum. His skin was warm and moist, and there were no petechiae. Moist rales were heard throughout both lung fields, but there was no dulness to percussion, and no signs of cavitation could be made out. The liver, the spleen and the lymph nodes were not enlarged. No other abnormalities were found on physical examination.

Laboratory Examination.—The red blood cell count was 3,700,000, hemoglobin 10.3 Gm. per hundred cubic centimeters and white blood cells 21,600, with polymorphonuclear cells 86 per cent (banded 35 per cent and segmented 51 per cent), lymphocytes 12 per cent and monocytes 2 per cent. The urine was normal. Smears and cultures of the sputum were thought to contain only the usual nasopharyngeal flora, and the presence of long slender branching gram-positive filaments was not considered significant. No acid-fast bacilli were recovered from the sputum by culture or guinea pig inoculation following concentration with sodium hydroxide. Cultures of the blood and urine gave negative results. Roentgenograms of the chest showed scattered infiltrations in the right upper lobe and in the left upper and lower lobes (fig. 1).

Course.—The course is graphically summarized in figure 2. Sulfadiazine was administered in full doses for a week, during which the temperature fell to normal and the patient felt much better. There was a relapse five days after adminis-

tration of the drug was stopped, with high fever and an increase in cough and sputum. Sulfadiazine was again given in full doses for nine days, and the temperature fell to normal on the sixth day of therapy. A second relapse occurred four days after treatment with the drug was discontinued, with high fever and a further exacerbation of cough and sputum. Roentgenograms showed a definite spread of the patchy infiltration of both lung fields, but on careful study of the sputum again no organism was recognized as the cause. The diabetes was well controlled with morning injections of 32 units of protamine zinc insulin and 16 units of crystalline zinc insulin, except when the temperature was elevated, when it was necessary to increase the protamine zinc insulin dose to 50 or 60 units. After ten days of high fever, sulfadiazine was administered, 6 to 8 Gm. a day for nine days, and the temperature gradually subsided to normal. In spite of this, the white blood cell count rose to 50,000, with 98 per cent polymorphonuclear leukocytes; cough and sputum continued, and the patient seemed to be getting worse. When the fever reappeared five days after the administration of sulfadiazine was stopped, a roentgenogram of the chest showed a further spread

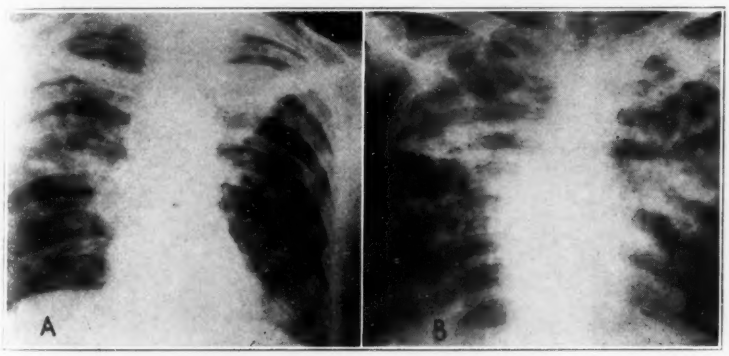

Fig. 1 (case 1).—*A*, appearance of chest on Feb. 26, 1943, showing scattered infiltrations in the upper lobe of the right lung and in the upper and lower lobes of the left. *B*, chest on May 10, 1943, showing extensive involvement of both lung fields.

of the infiltrations in both lung fields, especially in the upper half of the right lung, and a small amount of fluid was present at the base of the left lung. There appeared to be several small cavities in both lungs. Physical examination revealed coarse rales over both lung fields without definite signs of cavitation, and there was dulness at the base of the left lung. The liver and the spleen were not palpable, and there was no adenopathy.

Roentgen therapy, a total of 225 r, was given from April 26 to April 29 in view of the possibility that the infiltration in the lungs might be caused by atypical Hodgkin's disease. This was stopped when branching mycelial filaments, present in smears of the sputum since entry, were cultured and tentatively identified as a Streptothrix. At this time, firm, purplish nodules with fluctuant centers began to appear in the subcutaneous tissues all over the body, but were most prominent over the upper extremities, anterior part of the thorax and the abdomen. Some were fixed to the skin; others were deeper, and all were surprisingly free of tenderness. Thick greenish yellow pus was aspirated from

several of these nodules, and both smears and cultures contained the same organism that was isolated from the sputum. It was also isolated in pure culture from blood drawn on May 3.

It was now evident that the patient was suffering from a fungous infection of the lungs, with a diffuse hematogenous spread to the subcutaneous tissues, and presumably to other organs as well. He was weak and apathetic and ate little, requiring a drastic reduction of his insulin dose. The process continued to spread throughout both lung fields, and he was able to bring up only small amounts of sputum. The extensive involvement of both lungs, in contrast to the early infiltrations on entry, is clearly illustrated by reproductions of the roentgenograms of the chest of February 26 and May 10 (fig. 1).

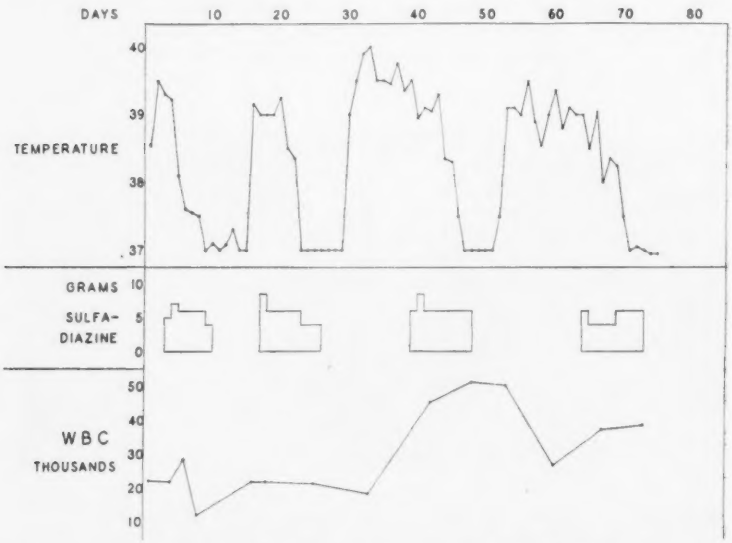

Fig. 2 (case 1).—Chart showing the beneficial effect of sulfadiazine on the temperature curve, and the considerable leukocytosis.

Four to 6 Gm. of sulfadiazine was given daily until he became oliguric, with a great amount of sulfadiazine and numerous red cells in the urine on May 9. The drug was stopped and fluids forced, and urine again flowed freely. The fever subsided, but he failed rapidly, became disoriented and then unconscious, and died on May 11.

Autopsy.—Examination seven hours after death revealed an emaciated elderly man with many firm to fluctuant nodules, 1 to 2 cm. broad, beneath the skin of the trunk, arms and legs which contained thick yellow-green exudate. None had developed sinuses. The pectoral, anterior abdominal and psoas muscles contained similar abscesses. The peritoneal and pleural cavities were free of fluid, but the latter were largely obliterated by dense adhesions.

Heart: The heart weighed 400 Gm. The myocardium of both ventricles contained several abscesses 3 to 10 mm. in diameter, some just beneath the intact epicardium

and others showing through the intact endocardium. The right ventricle was slightly dilated and hypertrophied. The coronary arteries and aorta were moderately atheromatous.

Lungs: The left lung weighed 1,430 Gm., and the right, 1,500 Gm. The ragged pleurae were irregularly thickened. Cut surfaces of both lungs were studded with yellow-gray opaque nodular areas of infiltration and abscesses up to 2 cm. in diameter, with thick yellow-green exudate in the centers (fig. 3).

Fig. 3 (case 1).—Photograph of the cut surface of the right lung, showing multiple abscesses up to 2 cm. in diameter.

Between these areas the lungs were wet and hyperemic. The peribronchial lymph nodes were large and black with occasional small abscesses.

Thyroid: The normal-sized gland contained a 1 cm. abscess in the left lobe. The parathyroids were normal.

Spleen: The spleen weighed 250 Gm. The capsule was smooth, and the cut surface firm and hyperemic, with a single 0.5 cm. subscapular abscess.

Kidneys: The kidneys weighed 200 Gm. each. The capsules stripped readily, leaving faintly granular surfaces with scattered abscesses from 2 to 15 mm. in diameter. On sectioning, these were found in both cortex and medulla. The pelves contained many fine crystals of sulfadiazine, and the intact mucosa was dull and hyperemic. The ureters were patent, and the bladder contained 500 cc. of turbid yellow urine.

Gastrointestinal Tract: The esophagus, the stomach, the appendix and the small and the large intestine were normal except for several 8 mm. abscesses in the wall of the midileum, which did not penetrate the mucosa or serosa, multiple false diverticula in the descending colon, and firm, almost black, feces in the colon.

The liver, the gallbladder, the adrenals, the pancreas, the prostate, the testes, the seminal vesicles and the vertebral marrow appeared normal.

Head: The scalp, the skull, the meninges and the brain were normal except for moderate atherosclerosis of the vessels of the circle of Willis. Multiple cut surfaces of the formaldehyde-fixed brain revealed no abscesses or abnormalities.

Microscopic Examination.—Lungs: The pleura was thickened with vascularized fibrous tissue. There were multiple abscesses in the lungs with necrotic debris, myriads of neutrophils and delicate gram-positive mycelial threads in the lumen. The alveolar septums had completely disappeared in these areas but were visible at the periphery, where the alveoli were filled with fibrin and neutrophils or fibroblasts and organized exudate containing lymphocytes, plasma cells and large mononuclear cells. In other areas, there were bronchopneumonic patches of fibrin, neutrophils and phagocytes with much nuclear debris, but no necrosis of the septums. Small bronchioles were entirely filled with purulent exudate. In several areas, moderately large blood vessels at the borders of abscesses were partially thrombosed and destroyed in the necrotizing process. Many alveoli were filled with edema fluid, and fairly large patches were well aerated.

Heart: The abscesses contained chiefly neutrophils in various stages of necrosis with walls of cellular fibrous tissue rich in lymphocytes, plasma cells and macrophages. The bordering myocardium showed fatty degeneration. The intima of branches of the coronary arteries was atherosclerotic.

Lymph Nodes: The peribronchial nodes were dark with carbon, and the sinuses contained many neutrophils and phagocytes. One node contained an abscess and another contained nodular fibrosis suggestive of healed tuberculosis.

Skin: Several sections contained discrete subcutaneous abscesses which had necrotic centers, myriads of neutrophils, and delicate beaded, branched gram-positive and gram-negative filaments 1 micron or less in diameter. These were best seen in the purulent exudate at the periphery of the abscess. There were no other bacteria. The filaments showed elongated oval thickening and were not acid-fast to acid-alcohol. The outer zone of the abscesses contained lymphocytes and large mononuclear cells.

Kidneys: The abscesses were as described in other tissues, and the adjacent tubules contained necrotic debris and neutrophils. Glomeruli showed no intercapillary sclerosis as seen at times in diabetes mellitus. The pelvis was largely denuded of epithelium, the submucosal vessels were hyperemic, and a small amount of purulent exudate covered the surface.

Pancreas: The islets were normal, but there was a mild increase in interacinar and interlobular fibrous tissue with moderate numbers of lymphocytes.

Brain: The brain and meninges were normal.

Abscesses in the spleen, ileum, thyroid and muscles were as described in other organs.

Culture of Heart Blood.—A blood culture taken from the heart at autopsy remained sterile after three months.

Mycology.—The slender branching myceliums found in the sputum (fig. 4 *C*), pus from the subcutaneous abscesses and the blood stream during life and from

multiple lesions at necropsy were gram-positive, finely and coarsely granular and were entirely decolorized by the acid-alcohol of Ziehl-Neelsen carbolfuchsin stain. They were weakly acid-fast when an aqueous solution of sulfuric acid was used for decolorization.[2a] The filaments were single or in small loose clusters without

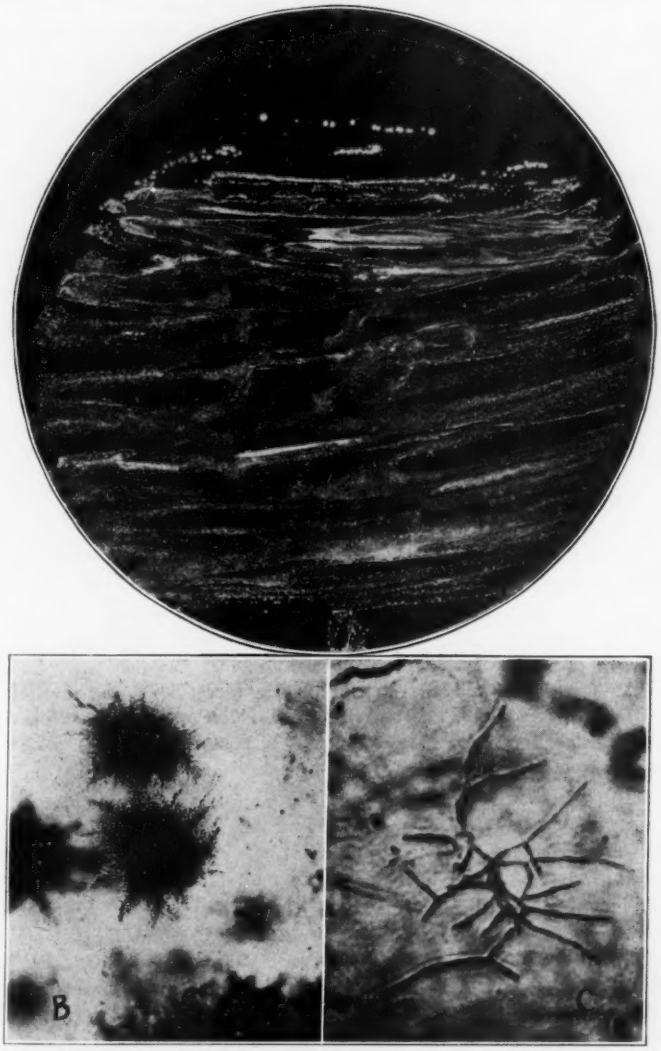

Fig. 4 (case 1).—*A*, photograph of culture of N. asteroides on nutrient agar, after two days (actual size). *B*, photomicrograph of culture of N. asteroides in a poured plate of nutrient agar showing the starlike colonies, after four days (× 110). *C*, photomicrograph of sputum stained by Gram's method showing branched mycelia (× 1,300).

club formation. Cultures of the subcutaneous abscesses and blood were pure and grew readily on blood agar, nutrient agar and Sabouraud's medium incubated aerobically at 37 C. In twenty-four hours there was a hazy growth on the plates, but in forty-eight hours the small white colonies, some smooth and glistening and others rough and dry, and all quite adherent to the medium, were as prominent as on the plate shown in figure 4*A*. When stained, they appeared as gram-positive bacillary and coccoid forms and as branched filaments, but when transferred to thioglycolate broth they grew as branching filaments in a pellicle on the surface. Within a week, some of the colonies on solid mediums were yellowish, and then became pale orange. There was a variation in the pigmentation of different colonies. Older cultures showed a white feathery surface. The starlike colonies described by Eppinger[1] are well illustrated in the poured agar plate (fig. 4*B*). This organism caused no change in litmus milk, and gelatin was not liquefied.

Cultures were submitted to Dr. C. W. Emmons, Principal Mycologist of the United States Public Health Service at the National Institute of Health, Bethesda, Md., and to Dr. N. F. Conant, Duke University School of Medicine, Durham, N. C., both of whom identified the organism as N. asteroides. Some of the tissues removed at necropsy were examined by Dr. Roger D. Baker, Duke University, who verified the presence of this organism in the lesions.

Summary.—The patient complained of a cough which was productive of much sputum, and lost weight. Roentgenograms showed infiltrations of both lungs. After three and a half months in the hospital, he died of a generalized infection due to N. asteroides with multiple metastatic abscesses apparently spread from the lungs. His sputum, subcutaneous abscesses and blood stream contained the fungus. He responded well to trials of sulfadiazine therapy, but, unfortunately, the etiologic agent was not recognized until too late in the course of the disease. His diabetes was probably favorable to the development and spread of the infection.

Case 2.—A white housewife of 49 entered Lane Hospital on April 3, 1945, because of headaches, nausea and vomiting for one month. Her father had died of diabetes mellitus at 44 and her son and daughter had had "nervous breakdowns." The patient had always been healthy except for influenza and pneumonia in 1919, following which bilateral deafness developed. Her fallopian tubes had been ligated, and the appendix removed in 1923. She lived in Stockton, in central California.

Present Illness.—She tired easily, required much rest and sleep and complained of frequent headaches for six months. Pounding occipital headaches, radiating to the left, became so severe during the last month that she was nauseated and vomited frequently. These attacks occurred most often during the night. Her vision failed, she became dizzy, and frequently she lost her balance in walking.

Physical Examination.—Her temperature was 37.8 C. (100.04 F.), her pulse rate 100, her respiration rate 20, her blood pressure 160 systolic and 100 diastolic, her height 157 cm. (62 inches) and her weight 81.8 Kg. (180 pounds). She was obese, complained bitterly of headaches and frequently expectorated small amounts of vomitus. The physical and neurologic findings on entry were negative, except for bilateral choked disks (4 D.), central scotomas and enlarged blindspots, engorged fundic vessels with some small hemorrhages around the disks and poor hearing. The gait was not tested because of nausea and headache on raising her head.

Laboratory Examination.—The red blood cell count was 6,600,000, hemoglobin 18.3 Gm. per hundred cubic centimeters and white blood cells 16,600, with polymorphonuclear cells 87 per cent (banded 4 per cent and segmented 83 per cent), lymphocytes 10 per cent and eosinophils 2 per cent. The Wassermann reaction of the blood was negative. The urine was normal. Roentgenograms of the skull showed no evidence of intracranial abnormalities.

Course.—Transient paresis of the right and left external rectus muscles developed, and her vision was subjectively worse. On April 6 she complained of unusually severe headache, her breathing was irregular, her fingers were cyanotic, and she lost consciousness for a few minutes, during which Hoffman's sign was bilaterally positive, Babinski's sign was negative, and reflexes of the upper extremities were hyperactive. A lumbar puncture showed an initial pressure of 270 mm. of water and a resting pressure of 215, with normal dynamics. The fluid was faintly bloody at first, but after less than 2 cc. was withdrawn it was clear and colorless. It contained 762 red blood cells, no white blood cells and 25 mg. of protein per hundred cubic centimeters; the Wassermann reaction was negative, and the colloidal gold test was read as 1223221100. She was often confused mentally and was noisy, and her headaches were poorly controlled by codeine. Ventriculography was contemplated, but on April 8, ten minutes after speaking lucidly to a nurse, she was found dead. Her blood pressure ranged from 220 systolic and 126 diastolic to 112 systolic and 80 diastolic during the five days that she was in the hospital, and her temperature gradually fell to 37 C. (98.6 F.). The clinical impression was an intracranial lesion, possibly a cerebral tumor or a vascular accident, with no localizing signs.

Autopsy.—Examination fifteen hours after death revealed a short, obese, middle-aged woman with an old white lower midline abdominal scar, subcutaneous lipomas on her ankles and no edema. The peritoneal and pleural cavities were free of fluid, but the midlateral area of the upper lobe of the right lung was adherent to the pleura.

Heart: The heart weighed 350 Gm. There was considerable subepicardial fat, and the chambers, valves, myocardium and coronary vessels were normal.

Lungs: Each lung weighed 450 Gm. All lobes were practically normal, except for slight edema and hyperemia and a localized area of slight pleural thickening with the adhesions described above. The peribronchial lymph nodes were normal but black.

Head: The scalp, skull, meninges and venous sinuses were normal. The brain weighed 1,350 Gm. The convolutions were smoothly flattened, and fluid was practically nil. The vessels of the circle of Willis were normal. The cerebellum showed distinct markings where it had been forced into the foramen magnum. An incision into a bulging fluctuant area in the posterior portion of the right lobe of the cerebellum caused thick greenish exudate to well forth. The exudate was semitranslucent and contained no granules. Sectioning of the cerebellum revealed an irregular 2.5 cm. abscess with a soft wall extending to within 1 cm. of the posterior medial border of the right lobe and not communicating with the fourth ventricle. The fluid in the normal-sized ventricles and in the foramen magnum was clear. The middle ears, mastoid cells and frontal, ethmoidal and sphenoidal sinuses appeared normal. Further sectioning of the formaldehyde-fixed brain revealed no other abnormalities.

Other abnormal findings at the autopsy were cholesterolosis of the gallbladder, a small mural fibromyoma of the uterus, multiple false diverticula and a small

pedunculated papilloma of the colon, moderate atherosclerosis of the aorta, absence of the appendix, and no other abscesses.

Culture of Heart Blood.—A blood culture taken from the heart at autopsy remained sterile.

Microscopic Examination.—Brain: The lumen of the cerebellar abscess was filled with necrotic exudate rich in neutrophils and filaments of gram-positive, branched, granular mycelia without clubs. Vascular granulation tissue, containing neutrophils, lymphocytes, vacuolated phagocytes and a few eosinophils formed the wall, with multiple small satellite abscesses. Beyond these, in some areas, there was an increase in fibrous tissue with lymphocytes and plasma cells, while in other areas fibrosis was absent and the inflammatory reaction diffusely blended into the adjacent brain substance. It extended into an outermost folium in one area, and here the meninges contained moderate numbers of lymphocytes and plasma cells and a few neutrophils. The meninges elsewhere in the cerebellum, medulla and cerebral cortex and the choroid plexus were normal; likewise sections from the parenchyma.

Lungs: Many alveoli contained thin edema fluid and debris, suggesting aspiration of gastric contents. The septal capillaries were hyperemic. A section from the area of adhesions over the midportion of the upper lobe of the right lung showed a flat subpleural zone of fibrous tissue surrounding many lymphocytes and hemosiderin-laden phagocytes with no tubercles or areas of suppuration.

Spleen: The splenic sinuses were hyperemic, with pools of blood, suggesting the asphyxial picture. The follicles were small. Moderate numbers of lymphocytes and plasma cells and a few eosinophils and neutrophils were in the pulp.

Bone Marrow: The vertebral marrow was normally active with a preponderance of cells of the myeloid series and many adult neutrophils.

Middle Ears: There was no evidence of inflammation.

Sections of other tissues and organs verified the gross findings and yielded no further pertinent information.

Mycology: Smears, cultures and microscopic sections from the cerebellar abscess showed dispersed branched filaments of a fungus which was identical with the N. asteroides described in case 1. It grew readily as a pure culture on ordinary mediums when incubated aerobically at 37 C. Like the organism of case 1, it was not acid-fast to acid-alcohol, but was weakly and irregularly acid-fast to aqueous sulfuric acid.

Summary.—The patient had severe headaches, nausea and vomiting for a month. She entered the hospital for study but died in five days with the clinical diagnosis of an intracranial lesion without localizing signs. Her temperature was practically normal, and there was a moderate neutrophilic leukocytosis. Autopsy revealed a large cerebellar abscess containing N. asteroides. The lungs must be considered as a possible primary focus even though only a small area of fibrosis with lymphocytes and pleural adhesions was found. The middle ears and mastoid cells were normal.

COMMENT

The fungi causing actinomycosis in man belong to two biologic types. The anaerobic type, A. bovis, is gram-positive and non-acid-fast and is found in approximately 90 per cent of the cases of clinical actinomycosis.[8] It usually produces "sulfur granules" in the tissues, made up of mycelial masses with radial club arrangement of the periphery. This club for-

mation is such a classic part of the description of this organism that in its absence the detection of Actinomyces may be confusing. The aerobic type includes several species, all of which are gram-positive and some of which are partially acid-fast. The latter may form granules without clubs or may be dispersed in branching filaments.[7] The aerobic N. asteroides is of this type and has been studied the most extensively. It is highly pathogenic for man. Benbow, Smith and Grimson [8] propose that since the signs, symptoms, course of the disease and response to treatment are so nearly identical in the two types of infection that the disease should be called actinomycosis.

Our case 1 illustrates the ease with which the presence of a pathogenic fungus may be disregarded in examinations of sputum and cause an unfortunate delay in arriving at the correct diagnosis. Although mycelia were seen in the smears, the organism was not successfully cultured on early attempts and was regarded merely as a harmless contaminant. It is not surprising that cultures and guinea pig inoculations gave negative results when the sputum was concentrated by the sodium hydroxide method, because N. asteroides is killed by this procedure.[8]

The gross and histologic appearance of the specific lesions in both of our cases were those of an acute pyogenic inflammation with a central zone of liquefactive necrosis and numerous polymorphonuclear leukocytes. There was no distinct caseation, no epithelioid tubercles and no giant cells. About the area of liquefaction was a zone of granulation tissue with neutrophils, lymphocytes and plasma cells and at times varying amounts of slightly more dense fibrous tissue. The dispersed mycelia of the fungus were not seen in the hematoxylin and eosin stains but were readily visible in the sections stained by Gram's method. The subcutaneous abscesses did not form fistulas or sinuses.

THERAPY

Since 1938, there have been many reports indicating the effectiveness of the sulfonamide compounds in the treatment of actinomycosis caused by A. bovis. These are summarized in the papers by Dobson, Holman and Cutting in 1941,[10] and by Dobson and Cutting in 1945.[11] The success of Benbow, Smith and Grimson [8] in curing 2 cases of actinomycosis caused by N. asteroides indicates that the sulfonamide compounds are equally effective in both the aerobic and the anaerobic type of this fungus. This is supported by a study of figure 2, which shows a striking correlation between the temperature curve and the

10. Dobson, L.; Holman, E., and Cutting, W.: Sulfanilamide in the Therapy of Actinomycosis, J. A. M. A. **116**:272 (Jan. 25) 1941.

11. Dobson, L., and Cutting, W.: Penicillin and Sulfonamides in the Therapy of Actinomycosis, J. A. M. A. **128**:856 (July 21) 1945.

administration of sulfadiazine in case 1. On four occasions, the high fever disappeared after sulfadiazine therapy, indicating that the drug was highly effective against N. asteroides. This was not appreciated until after the third course of sulfadiazine when the entire temperature and therapy records were charted on a single sheet on paper. Had the attending staff been fully aware of the beneficial action of the sulfadiazine, the therapy would have been altered, for it has become axiomatic that the best results in actinomycosis follow prolonged intensive sulfonamide medication. When the diagnosis was finally established the disease was so widespread that intensive therapy was of no avail.

A few reports suggest that penicillin is effective in actinomycosis, but none of the patients have been followed sufficiently long to be certain that relapses will not occur. Dobson and Cutting [11] used sulfonamide or penicillin therapy in 16 cases and considered the disease cured in 7 cases and arrested in 7. In 3 cases the disease was reported cured or arrested by penicillin alone, in 3 arrested by penicillin and sulfadiazine and in 6 cured by sulfonamide drugs. In 2 cases in which the latter medication was given, the disease ended fatally. In 1 of the 3 cases in which penicillin alone was given, an apparent cure of cervicofacial actinomycosis was effected by the administration of 4,655,000 units over a thirty-eight day period. Rapid healing in another case of cervicofacial actinomycosis followed the use of 1,560,000 units of penicillin in seventeen days. The third was a case of pulmonary and retroperitoneal actinomycosis in which 4,300,000 units of penicillin in thirty-seven days produced a prompt and decided improvement, so that the disease was considered arrested. They concluded that both penicillin and the sulfonamide compounds are highly effective drugs in the treatment of actinomycosis. There are as yet no reports on the use of penicillin in actinomycosis due to N. asteroides.

In vitro tests, made by streaking a broth culture of the N. asteroides isolated from our case 1 onto blood agar plates containing varying concentrations of penicillin, revealed that the organism grew as readily in the presence of .05, 0.1, 0.4, 1, 2 and 4 units per cubic centimeter as on the controls. Experience with other infectious diseases indicates that organisms which are resistant to as high concentrations of penicillin as 1 unit per cubic centimeter do not respond well to penicillin therapy in the usual doses. If 0.5 units per cubic centimeter is considered a high therapeutic level for penicillin it would appear from the tests in vitro that eight times this concentration would have no inhibitory effect on the growth of the organism. However, this relationship may be altered by the natural protective mechanisms of the body so that a lesser level may become effective. The results obtained by Dobson and Cutting [11] in patients infected with the anaerobic type of this fungus indicate that

penicillin in large doses should be given a thorough trial in patients infected with the aerobic type.

SUMMARY

Infections in man due to the aerobic, partially acid-fast Nocardia asteroides are rare as compared to those due to the anaerobic Actinomyces bovis. The symptoms, course of the disease and response to therapy are so nearly alike that the disease produced by the two types of fungi should be called actinomycosis. Thirty-two cases of infection with N. asteroides have been collected from the literature. The mortality rate appears to be high: 28 of 32 patients were dead at the time the reports were published. The infection was pulmonary in 28 cases, and the brain was the site of metastasis in at least 10. In 2 cases infection of the lungs and the chest wall was apparently cured by surgical drainage, sulfonamide therapy iodides and roentgen therapy.

Two new cases of infection with N. asteroides are added in this report. The first of these was of a man of 63, who was hospitalized for three and a half months for cough, sputum, loss of weight and pulmonary disease. He responded well to trials of sulfadiazine therapy, but the etiologic agent was not recognized until late, when the fungus was isolated from his sputum, subcutaneous abscesses and blood stream. At autopsy the lungs, peribronchial lymph nodes, heart, thyroid, kidneys, spleen, intestines, muscles and subcutaneous tissues contained abscesses produced by N. asteroides. The second case was that of a woman of 49, who was hospitalized for five days prior to death with a clinical diagnosis of an intracranial lesion without localizing signs. Autopsy revealed an abscess in the cerebellum caused by N. asteroides. The lungs are suspected as the primary focus, and no other metastases were found.

It is recommended that patients with actinomycosis due to the aerobic N. asteroides be treated with the sulfonamide compounds, and penicillin, as vigorously as are those infected with the anaerobic A. bovis, and that surgical drainage, iodides and roentgen ray therapy be used as the indications arise.

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Progress in Internal Medicine

SYPHILIS

A Review of the Recent Literature

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IN THIS annual review [1] of the recent developments in the field of syphilology, emphasis is placed on subjects of greatest current importance. The publications that appeared from July 1945 to June 1946 are concerned for the most part with research carried on during the years of the war. The prodigious cooperative study of penicillin therapy under the supervision of the wartime Committee on Medical Research; the development under war-borne emergency of dimercaprol ("BAL"; 2,3-dimercaptopropanol), efficacious in the treatment of arsenical poisoning; increased understanding of biologic false positive reactions to serologic tests for syphilis, and advancements in civilian and military control of syphilis—all these bear the imprint of the war stimulus to scientific advancement. The number of journals available for review from war-devastated Europe is negligible.

NEW BOOKS ON SYPHILIS

Merritt, Adams and Solomon [2] are the authors of a recently published monograph on neurosyphilis, based largely on their extensive

From the United States Public Health Service and the Johns Hopkins University Venereal Disease Research and Postgraduate Training Center.

1. (*a*) Moore, J. E.: Syphilis: A Review of the Recent Literature, Arch. Int. Med. **56**:1015 (Nov.) 1935. (*b*) Padget, P., and Moore, J. E.: Syphilis: A Review of the Recent Literature, ibid. **58**:901 (Nov.) 1936; (*c*) **60**:887 (Nov.) 1937. (*d*) Padget, P.; Sullivan, M., and Moore, J. E.: Syphilis: A Review of the Recent Literature, ibid. **62**:1029 (Dec.) 1938. (*e*) Moore, J. E., and Mohr, C. F.: Syphilis: A Review of the Recent Literature, ibid. **64**:1053 (Nov.) 1939. (*f*) Mohr, C. F.; Padget, P., and Moore, J. E.: Syphilis: A Review of the Recent Literature, ibid. **66**:1112 (Nov.) 1940. (*g*) Mohr, C. F.; Padget, P.; Hahn, R. D., and Moore, J. E.: Syphilis: A Review of the Recent Literature, ibid. **69**:470 (March) 1942. (*h*) Reynolds, F. W.; Mohr, C. F., and Moore, J. E.: Syphilis: A Review of the Recent Literature, ibid. **70**:836 (Nov.) 1942; (*i*) **72**:635 (Nov.) 1943. (*j*) Mohr, C. F.; Scott, V.; Hahn, R. D.; Clark, E. G., and Moore, J. E.: Syphilis: A Review of the Recent Literature, ibid. **74**:390 (Nov.) 1944. (*k*) Mohr, C. F.; Scott, V.; Hahn, R. D., and Moore, J. E.: Syphilis: A Review of the Recent Literature, ibid. **77**:332 (March); 428 (April) 1946.

and collective experiences at the Boston City Hospital and the Boston Psychopathic Hospital. The approach to the subject is that of the neuropsychiatrist well versed in neuropathology. The various clinical syndromes of neurosyphilis are correlated with the underlying histopathologic changes in the central nervous system in a manner superior to any heretofore available. The discussion of therapy is, however, inferior to the chapters on the clinical and neuropathologic phases.

EXPERIMENTAL SYPHILIS

The albino house mouse (Mus musculus) has long been known to be a susceptible carrier of experimental syphilis to rabbits. German investigators have reported that several such European rodents may be used to perpetuate strains of Treponema pallidum. These observations led Wile and Johnson [3] to determine whether mice in this country could be as readily infected. Five different species of native American mice were inoculated intraperitoneally with the Nichols strain of T. pallidum (a saline suspension of rabbit testicular syphiloma). All five were found to be capable of harboring the organisms, as determined by inoculations of rabbits, although in the mice the infection uniformly was symptomless.

Wile and Johnson [4] also have studied experimentally the course of syphilis in golden hamsters. Syphilis in this animal inoculated with the Nichols strain of T. pallidum ran a course similar to that in white mice, i. e., the infection remained clinically inapparent, dark field examination of organs gave negative results, silver impregnation stains revealed no spirochetes, hematoxylin stains showed no histologic changes characteristic of syphilis and the Kahn serologic reaction did not become positive. When, however, tissues (brain, testis or pooled liver, spleen, gonads and heart) from hamsters infected by the intraperitoneal route were inoculated intratesticularly into rabbits, typical syphilomas developed.

SERODIAGNOSIS OF SYPHILIS

Quantitative Serologic Tests.

The importance of quantitative serologic tests for syphilis again is stressed by Callaway,[5] who has found titered tests most helpful in

2. Merritt, H. H.; Adams, R. D., and Solomon, H. C.: Neurosyphilis, New York, Oxford University Press, 1946.

3. Wile, U. J., and Johnson, S. A. M.: Experimental Syphilis in Different Species of Native American Mice, Am. J. Syph., Gonor. & Ven. Dis. **29**:416 (July) 1945.

4. Wile, U. J., and Johnson, S. A. M.: Experimental Syphilis in the Golden Hamster, Am. J. Syph., Gonor. & Ven. Dis. **29**:418 (July) 1945.

5. Callaway, J. L.: Importance of Quantitative Serologic Tests for Syphilis, South. Med. & Surg. **107**:273 (Aug.) 1945.

(1) study of questionable biologic false positive reactions, (2) serologic follow-up of children born of syphilitic mothers, (3) exclusion of the possibility of "zone" phenomena, (4) measurement of the effects of therapy and (5) prediction of the imminence of clinical relaspe, which so often is preceded by serologic relapse.

Newer Serologic Procedures.

The "Optimal Zone Reaction."—Kahn [6] has made a preliminary report of a serologic procedure which he calls the "optimal zone procedure," designed to supplement current serodiagnostic tests. This test is based on an extension of the serum: antigen ratios from 3, used in the standard Kahn test, to 10 or even 15 ratios. By the use of these additional ratios, positive results were obtained in cases of known syphilis which gave seronegative reactions by the usual tests. Also, the author states the belief that negative results with the new procedure following antisyphilitic therapy may be more reliable as an indication of "cure" than negative results with current serodiagnostic tests.

Cardiolipin Antigen.—Improvements in the preparation of cardiolipin antigen [7] continue to be reported. Pangborn herself [8] has further simplified the procedure for isolating the subtance. The method depends on the fact that cardiolipin is acidic and readily forms stabile salts, which may be converted one to another and impurities removed by utilization of the differing solubilities of the several salts in various combinations of solvents. Solutions of cardiolipin may be standardized on the basis of their phosphorus content.

Standard antigens with iodized poppyseed oil for serodiagnostic tests for syphilis, even those prepared under the most carefully controlled conditions, have been subject to variation in sensitivity and specificity. The isolation of cardiolipin from beef heart and the development of methods for the purification of lecithin give promise of antigens whose components can regularly be reproduced. Rein and Bossak [9] report that cardiolipin antigen, composed of cardiolipin (0.2 per cent) and lecithin (1.3 per cent), may be successfully adopted for use in a microflocculation slide test for the serodiagnosis of syphilis. The sensitivity of this antigen was higher than that obtained with Kline diagnostic, Mazzini, Kahn and Kolmer tests as performed at the Army Medical

6. Kahn, R. L.: Optimal Zone Reaction in the Diagnosis and Treatment of Syphilis, Arch. Dermat. & Syph. **53**:633 (June) 1946.

7. Pangborn, M. C.: Isolation and Purification of a Serologically Active Phospholipid from Beef Heart, J. Biol. Chem. **143**:247 (March) 1942.

8. Pangborn, M. C.: A Simplified Preparation of Cardiolipin, with a Note on Purification of Lecithin for Serologic Use, J. Biol. Chem. **161**:71 (Nov.) 1945.

9. Rein, C. R., and Bossak, H. N.: Cardiolipin Antigens in the Serodiagnosis of Syphilis: A Microflocculation Slide Test, Am. J. Syph., Gonor. & Ven. Dis. **30**:40 (Jan.) 1946.

Center. This increased sensitivity was obtained without apparent increase in nonspecificity. The specificity of cardiolipin antigen in the presence of malarial infection is described as being "extraordinary," but with serums from patients with leprosy or infectious mononucleosis increased specificity was not apparent.

Kline [10] states the belief that, if further experience confirms the excellent results thus far obtained with cardiolipin antigen, it may be possible to develop a single standard flocculation test for syphilis. In his experience, involving over 2,500 serum tests (including 270 in cases of malaria, over 1,600 on patients with other conditions and over 650 in cases of syphilis), flocculation tests with cardiolipin antigen gave more specific results in nonsyphilitic patients than did Eagle, Hinton, Kahn, Kline and Mazzini antigens and more sensitive results in cases of syphilis than Kline antigen.

Spectrophotometry in Serodiagnosis.—Spectrophotographic methods, now of considerable importance in many branches of chemistry, recently have been applied to serodiagnostic procedures. Of the numerous methods proposed for the standardization of complement, Mayer, Eaton and Heidelberger [11] prefer the spectrophotometric procedure for determining complement in terms of "the 50 per cent hemolytic unit." This procedure, they believe, eliminates uncertainties due to subjective factors and furnishes precise and reproducible determinations of complement activity.

Spiegel-Adolf [12] has utilized spectrophotometry in studies of the cerebrospinal fluid. Since most spinal fluids are colorless, spectrographic methods with ultraviolet light must be employed. Three groups of known body constituents absorb ultraviolet light: proteins, lipids and nucleic acids. These substances, therefore, can be detected in the cerebrospinal fluid by ultraspectrophotographic methods. Preliminary studies suggest the presence in the cerebrospinal fluid of patients with dementia paralytica of proteins not normally present in this fluid.

Spinal Fluid Proteins.—Lange [13] has studied the colloidal gold reaction by analyzing the physicochemical factors involved and by testing various combinations of protein fractions. When various protein fractions were mixed with gold sol in the presence or absence of electrolytes

10. Kline, B. S.: Cardiolipin Antigen in the Microscopic Slide Precipitation Test for Syphilis, Am. J. Clin. Path. **16**:68 (Feb.) 1946.

11. Mayer, M. M.; Eaton, B. B., and Heidelberger, M.: Spectrophotometric Standardization of Complement for Fixation Tests, J. Immunol. **53**:31 (May) 1946.

12. Spiegel-Adolf, M.: Ultraspectrographic Studies on Cerebrospinal Fluid, Confinia neurol. **7**:77, 1946.

13. Lange, C.: Theory of the Colloidal Gold Reaction: I. Reactions Between Gold Sol and Isolated Protein Fractions, J. Lab. & Clin. Med. **30**:1006 (Dec.) 1945.

and at p_H 7.4, three qualitatively different reactions were observed: protection, sensitization and coagulation. 1. Protection is produced both by albumins and normal serum globulins in the prezone and by hemoglobin at a p_H above its isoelectric point. 2. Sensitization is produced by serum globulin within an optimal range, electrolytes being required to complete the coagulation. 3. True coagulation, without the assistance of electrolytes, is produced in cerebrospinal fluid only by the pseudoglobulin-like *degenerative protein*[14] indicative of parenchymatous degeneration which elicits the so-called paretic, or plateau, curve.

The author states the belief that the plateau curve is fundamentally different from prezone curves. The latter, in the absence of a *true coagulator*,[14] result from qualitative and quantitative differences of the globulins, while the albumins, as protectors, have only a quantitatively decreasing effect. He also controverts the widely adopted hypothesis that differences in the colloidal gold reaction are produced by alterations in the albumin-globulin ratio. His interpretation is that the changes are regulated by qualitative and quantitative differences in the globulins. The removal of albumins from cerebrospinal fluids, so that any effect of the albumin-globulin ratio is eliminated, produced no qualitative change either in the paretic curve or in the prezone curves.

It has been suggested that a determination of the albumin-globulin ratio in the cerebrospinal fluid might replace the colloidal tests. Several methods have been devised for determining this ratio, all based on the assumption that the globulin present in cerebrospinal fluid is precipitated by 50 per cent saturation with ammonium sulfate. Lange[15] also presents data to indicate that this assumption is true only when considerably higher concentrations of protein than those in normal spinal fluid are present. With relatively low concentrations of protein, which prevail in neurosyphilis, misleading results are obtained by use of 50 per cent saturation with ammonium sulfate to precipitate the globulin. Electrophoretic methods are accurate, but they require such large quantities of spinal fluid as to make them unfeasible in routine practice. With methyl alcohol precipitation, however, Lange expresses the opinion that it is possible to determine consistently accurate albumin-globulin ratios in cerebrospinal fluids both in normal persons and in those with various neurologic diseases. The author emphasizes that the spinal fluid albumin-globulin ratio should be interpreted as an integral part of a complete examination of spinal fluid. He states the belief that the ratio provides information regarding the permeability of the meninges.

14. Italics are Lange's.

15. Lange, C.: Interpretation of Findings in the Cerebrospinal Fluid: II. The Technique and Systematic Interpretation of the Albumin-Globulin Ratio in Cerebrospinal Fluids, J. Lab. & Clin. Med. **31**:552 (May) 1946.

Biologic False Positive Reactions to Serologic Tests.

A review of the entire subject of biologic false positive reactions for syphilis recently has been made by Beerman.[16] This extensive discussion does not lend itself readily to condensation, and the reader is referred to the original article.

The use of mass blood testing as a means of finding syphilis is a time-tested and acceptable procedure in control of syphilis. However, in any mass survey the frequent occurrence of false positive reactions poses a problem of considerable magnitude.

Stokes and his co-workers[17] have summarized the results of an investigation and follow-up on applicants as American Red Cross blood donors found to have positive serologic reactions for syphilis. Of these, only 40.5 per cent were finally adjudged to have syphilis; the remainder (59.5 per cent) were believed to have biologic false positive reactions. In the process of evaluation described, the decision that syphilis actually was present was reached within three months in 69.2 per cent; among those adjudged to have false reactions, the decision was reached within that time in only 22 per cent.

In the differentiation of syphilitic from nonsyphilitic reactions, the authors stress the value of an interpretation of the results of a battery of simultaneously performed sensitive flocculation and complement fixation tests. It was found that the syphilitic positive reaction tended to be of high titer and consistently positive on multiple repetition, with results of precipitation and complement fixation tests confirming each other. The nonsyphilitic reaction was usually of low reagin titer, weakly positive or doubtful but fluctuant, sometimes strongly positive, inconsistent as between flocculation and complement fixation tests, usually more strongly positive in the former than the latter, and tending toward negativity within three months.

In their experience, repeated and carefully interpreted serologic tests were of more value than clinical history, physical examination, heterophile tests, roentgenograms of the chest and study of the patient's family. When clinical evidence of syphilis was present, congenital syphilis and neurosyphilis were the two chief clinical types uncovered by mass serologic testing. The study indicates that with the sensitive modern serodiagnostic tests routine mass blood testing will unearth a disconcertingly high proportion of biologic false positive serologic reactions.

In an effort to determine whether a differentiation between positive serologic reactions due to syphilis and those due to other factors is

16. Beerman, H.: Biologic False Positive Reactions to the Tests for Syphilis, Am. J. M. Sc. **209**:525 (April) 1945; **210**:524 (Oct.) 1945.

17. Stokes, J. H.; Boerner, F.; Hitchens, A. P., and Nemser, S.: Nonspecific Reactions in Routine Blood Testing for Syphilis, J. A. M. A. **130**:57 (Jan. 12) 1946.

possible with serologic methods now available, Scott and his fellow workers [18] have investigated, in over 1,000 specimens of serum: (*a*) the "serologic pattern" of acquired and congenital syphilis and of biologic false positive reactions; (*b*) the serologic reactions of syphilitic and falsely positive serums against nonspecific antigens, and (*c*) the possible differentiation of truly positive (syphilitic) from biologic false positive reactions by three special serologic procedures (the Kahn "verification" test, a special technic originated by one of the authors [Rein], and the spirochetal complement fixation test).

Under the conditions of the study, which are described in detail, it appeared that:

> . . . there is no "serologic pattern" with the tests employed which serves to differentiate "true" from "false" reactions or one type of syphilitic infection (congenital) from another (acquired); that "false positive" sera do not react with nonspecific antigens to a greater extent than do syphilitic sera; and that special, supposedly verifying techniques (Kahn, Rein, spirochetal complement-fixation tests) do not serve to differentiate "true" from "false" positive reactors. As to the latter, on the contrary, it was demonstrated that for all three of these special techniques as employed in this experiment, the type of reaction obtained was a function of the reagin content of the particular serum tested. Low-titered sera, whether from syphilitic or false positive reactors, tended to give the biologic type of reaction with the Kahn "verification" test and Rein special technique, and negative or doubtful results with the spirochetal complement-fixation test; high titered syphilitic sera tended to give the syphilitic type of reaction with the Kahn and Rein tests and positive spirochetal complement-fixation tests; and this correlation between titer and type of reactivity held for at least one animal species (cows). . . .
>
> The results of this, as of previous studies, indicate that biologic false positive sera are usually (though not always) of low titer. Unfortunately, this is not a valid differential point, since the same is true of many patients with syphilis previously treated or untreated, especially the former.
>
> With presently available serologic techniques, therefore, the diagnosis of "true" versus "false" positivity could not be established by examination of a single specimen of serum, either by any single test, "verification" or otherwise, or by any combination of tests. New serologic methods should be developed. Until this is done differential diagnosis between syphilis and other "reagin producing" diseases must continue to be attempted by painstaking clinical examination of the patient, by the weighing of epidemiologic factors (opportunity for infection, examination of sexual and familial contacts), and by serial quantitative serologic tests, repeated over a period of days, weeks, months, or in some cases years.

False Positive Reactions Following Blood Donation.—During World War II there were received from various American Red Cross blood donor centers reports to the effect that occasionally blood donation appeared to result in the transitory appearance of syphilitic reagin in

18. Scott, V.; Rein, C. R.; Schamberg, I. L.; Moore, J. E., and Eagle, H.: The Serologic Differentiation of Syphilitic and False Positive Sera, Am. J. Syph., Gonor. & Ven. Dis. **29**:505 (Sept.) 1945.

the blood of donors. During the war the number of blood donors in the United States ran into the millions. With the increasingly widespread use of routine serologic tests and the zeal with which many physicians institute antisyphilitic therapy on the sole basis of one or more positive reactions, it was important to determine whether blood donation per se may be responsible for the appearance of serologically detectable amounts of reagin in the serum of donors. Unfortunately, despite extensive consideration by the Subcommittee on Venereal Diseases of the National Research Council and several studies under governmental auspices, the situation remains unclarified.

From the statistical analysis of Boynton,[19] it is readily apparent that the incidence of false positive reactions among blood donors cannot be correlated with the actual number of venesections per donor. No clinical data were available on the donors included in this study, although it assumed that those with even temporarily suspicious reactions largely

Data on Positive Serologic Reactions in Presumably Nonsyphilitic Blood Donors (Barnard, Rein and Doan [20])

Positive Serologic Reversal (Sic) Following	Number	Donors in Category	Per Cent	
First donation	12	11,299	0.106	
Second donation	11	7,604	0.144	
Third donation	6	5,709	0.105	0.413
Fourth donation	2	3,445	0.058	
Fifth donation	0	1,885	0.000	

were self excluded after the first donation following which the question of syphilis arose.

Barnard, Rein and Doan [20] have studied the possible role of blood donation as a factor in producing positive serologic reactions in presumably nonsyphilitic donors. Their data are based on groups of American Red Cross blood donors whose positive serologic reactions subsequently were found spontaneously to revert to negative.

A summary of their data, reproduced in the table, indicates that there was a slightly higher percentage incidence of false positive reactions among second time donors than among first time donors and that after the third donation false positive reactions continued to appear, but with diminishing frequency. The authors admit that an incidence of 0.4 per cent is flimsy evidence on which to base a conclusion that

19. Boynton, M. H.: The Incidence of Positive Serologic Reactions in Multiple Blood Donors, Am. J. Syph., Gonor. & Ven. Dis. **30**:252 (May) 1946.

20. Barnard, R. D.; Rein, C. R., and Doan, C. A.: False Positive Serologic Tests for Syphilis Following Blood Donation, Am. J. Syph., Gonor. & Ven. Dis. **30**:255 (May) 1946.

phlebotomy may cause biologic false positive reactions for syphilis. They accept, however, the questionable statistical validity of their findings, pointing out that the incidence of positive reactions probably would have been higher but for factors of self selection and "weeding out" of actual and potential reactors. Of greater significance, however, is the fact that presumably nonsyphilitic persons have been observed in whom the usually accepted postulates for demonstration of a causal relationship between a nonsyphilitic medical episode (blood donation) and positive serologic reactivity have been fulfilled, i. e. (*a*) initial seronegativity, (*b*) confirmed seropositivity without other known cause and (*c*) spontaneous reversal to negativity.

Boerner, Nemser and Stokes [21] were unable to demonstrate any significant effect of phlebotomy or of repeated blood donation on quantitative serologic reactions for syphilis. One hundred and twenty-eight prison inmates were the donors. When quantitative complement fixation and quantitative flocculation tests were done immediately before and immediately after withdrawal of 500 cc. of blood, no significant difference in reagin content of the serum was observed. Ninety-seven of these donors were also tested at intervals from the fifth to the fifteenth day following phlebotomy. In none was there any significant change in the serologic reactions. Summarizing their results, the authors state:

> Within the limits imposed by the conditions of the experiment, including the limited number of donors used, and by possible confusing elements such as intercurrent infections or other known causes of biologic false positives, and the fallibility of the clinical examination for syphilis as performed, it can certainly not be said that this series reveals the existence of a non-specific positive due to multiple blood donation, or to bleeding as such. Neither can it be said that such a possibility is totally excluded.

Thus, the published reports are at variance, and, on the basis of presently available information concerning the question of whether biologic false positive reactions occur as a result of blood donation alone, the only verdict now possible is one of "insufficient proof."

False Positive Reactions in Malaria.—Biologic false positive reactions to complement fixation tests for syphilis are frequent in the course of malaria. They occur most frequently, according to Babin and Dulaney,[22] in a period of six to ten days following an attack of malaria. Interestingly enough, not only does malaria cause false positive serologic reactions for syphilis, but also syphilis causes false positive reactions in the recently developed complement fixation tests for malaria that utilize as antigen

21. Boerner, F.; Nemser, S., and Stokes, J. H.: A Study of the Effect of Bleeding and of Repeated Blood Donation on Serologic Tests for Syphilis, Am. J. M. Sc. **211**:571 (May) 1946.

22. Babin, F., and Dulaney, A. D.: Complement Fixation in Malaria and Syphilis, Am. J. Hyg. **42**:167 (Sept.) 1945.

a phosphate buffer extract of Plasmodium knowlesi. Quantitative serologic tests for both syphilis and malaria were performed on specimens of serum from 22 syphilitic patients under treatment with inoculation malaria. In all cases, the reaction to the complement fixation test for malaria became positive, the titer paralleling the parasite count. Eighteen (82 per cent) of the patients also showed a rise in Wassermann titer coincident with and in proportion to the degree of positivity observed with the complement fixation test for malaria. The nature of the interreactivity observed in the complement fixation tests for syphilis and malaria has not been established, but these authors suggest two possible explanations: (1) that there is a common or closely related antigenic component in the antigens which are responsible for the cross reaction and (2) that malaria activates syphilitic infections, the increased titer of serologic tests for syphilis occurring during malaria representing an anamnestic reaction.

Robinson and McKinney[23] have performed tests on the blood serum for syphilis and have examined the spinal fluids of 100 nonsyphilitic white men with Plasmodium vivax malaria. Weekly tests of the blood were done on all patients with positive or doubtful reactions to Kahn tests until seronegativity was reestablished. Positive reactions to tests of the blood were found in 35 per cent of this group of patients, and an additional 11 per cent had doubtful reactions. There was no apparent correlation between the number of attacks of P. vivax malaria and the development of biologic false positive reactions to serologic tests for syphilis. The majority of positive reactors were seronegative within four weeks and all by the end of eleven weeks. Of especial interest is their negative report so far as the spinal fluid is concerned. In no instance was the spinal fluid cell count elevated, nor were there any positive Kahn reactions of the spinal fluid.

Tuberculosis.—The results of a study of 100 infants with various serious manifestations of tuberculosis in relation to occurrence of false positive serologic reactions for syphilis are reported by Sellek Azzi and del Frade.[24] Falsely positive reactions for syphilis were obtained in from 3 to 4 per cent of these tuberculous infants. Of special interest is the fact that 18 per cent of 50 patients with tuberculous meningitis had false positive reactions to tests of the spinal fluid for syphilis.

Infections of the Respiratory Tract.—Florman and Weiss[25] have examined serial specimens of serum from 68 patients with a clinical

23. Robinson, H. M., Jr., and McKinney, W. W.: Vivax Malaria and Serologic Tests for Syphilis, J. A. M. A. **129**:667 (Nov. 3) 1945.

24. Sellek Azzi, A., and del Frade, A.: Porcentaje y naturaleza de las reacciones falsas positivas de sífilis en tuberculosis, Bol. Soc. cubana de pediat. **17**: 159 (May) 1945.

(Footnotes continued on next page)

diagnosis of primary atypical pneumonia for the presence of four different antibodies: cold agglutinins, indifferent streptococcus agglutinins, elementary body type virus complement-fixing antibodies and reagin, the reacting substance in serodiagnostic tests for syphilis. Six of 36 patients tested (17 per cent) had transiently positive serologic reactions for syphilis during convalescence from primary atypical pneumonia. Six other patients had transiently doubtful reactions. There was no apparent correlation between the occurrence of other positive reactions (cold agglutinins, streptococcus agglutinins or elementary body virus antibodies) and the occurrence of biologic false positive serologic reactions for syphilis.

Lymphogranuloma Venereum.—The occurrence of biologic false positive reactions to serologic tests for syphilis in certain cases of lymphogranuloma venereum has been described. The hyperproteinemia associated with this condition has been suggested, but never proved, to be the cause. Heymann and Webb [26] have studied in 25 patients with proved lymphogranuloma venereum the results of serologic reactions for syphilis, formol-gel reactions and determinations of serum protein. Thirteen patients had concomitant syphilis, and, of the remaining 12, there were 3 with biologic false positive serologic reactions. There was no correlation between the occurrence of false positive reactions and hyperproteinemia. They appeared to be related to the activity of the lymphogranuloma venereum infection and usually persisted from two to three weeks, reverting to negative as the bubos healed.

Chickenpox.—Kane and Henneman [27] have added chickenpox to the list of the conditions which may produce biologic false positive reactions to serologic tests for syphilis. Among 22 patients with chickenpox, five transiently positive reactions to Hinton flocculations tests were observed, 1 of the patients also having a transiently positive Kahn reaction. In no case was the reaction to the Wassermann complement fixation test positive. All but 1 of the patients in whom positive reaction to Hinton tests developed were young college students, in whom there was no reason to suspect syphilis. The earliest positive reaction developed seven days after the onset of the eruption and in 1 case persisted for fifty-one days. This series is too small to reflect the true incidence of biologic false positive reactions in chickenpox, but the findings suggest that they are not infrequent, at least with the Hinton modification of the flocculation test.

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25. Florman, A. L., and Weiss, A. B.: Serologic Reactions in Atypical Pneumonia, J. Lab. & Clin. Med. **30**:902 (Nov.) 1945.

26. Heymann, A., and Webb, E. L.: False Positive Serologic Reactions for Syphilis in Lymphogranuloma Venereum, J. Ven. Dis. Inform. **27**:122 (May) 1946.

27. Kane, L. W., and Henneman, P. H.: False-Positive Hinton Reactions Following Chicken Pox, New England J. Med. **233**:407 (Oct. 4) 1945.

Erythema Nodosum.—Löfgren [28] suggests that biologic false positive serologic reactions for syphilis may occur in association with erythema nodosum. The cases described were part of a larger series being studied from the standpoint of etiology and pathogenesis of erythema nodosum. Among 178 patients, there were 7 with positive serologic reactions for syphilis considered to be nonspecific.

Seroresistance.

So frequently is the consultant syphilologist called on to explain to the patient (and all too often to his doctor as well) the phenomenon of persistent seropositivity that Moore [29] has recorded in dialogue form an imaginary conversation between a seroresistant patient and his physician, deliberately so designed that reprints of the article may be handed to patients and sent to their family physicians in order to supplement the lengthy interviews and the equally lengthy letters which now are so necessary. The printed word never can replace the personal contact between physician and patient, though it is believed that a preliminary reading of this discussion by a worried seroresistant patient will form the basis for a more satisfactory and individualized consultation. Physicians occasionally faced with the problem of persistently positive reactions to serologic tests following adequate therapy for late (especially latent) syphilis will find this discussion well worth reading. Consultant syphilologists may well utilize this device or some modification of it based on their own experience as a time-saving and effective educational expedient.

CLINICAL MANIFESTATIONS

Early Syphilis.

Primary Lesions.—As Tello [30] points out, the frequency of asymptomatic infections in women is more apparent than real, becoming less frequent as greater care is used in examination, especially of the cervix. Chancre of the cervix must be sought to be identified. These lesions, according to the author, may be superficial erosions, deeper ulcerations or vegetating lesions. Cervical secretions or menstrual blood may contain the spirochetes of syphilis either in the presence or in the absence of visible lesions.

Hazen [31] has contrasted the Negro and white races in respect to the incidence of extragenital syphilitic infection. In his experience, only

28. Löfgren, S.: False Positive Seroreactions for Syphilis in Connection with Erythema Nodosum, Acta dermat.-venereol. **26**:243 (Jan.) 1946.

29. Moore, J. E.: Seroresistance (Wassermann-Fastness) in Syphilis: A Discussion for the Patient, Am. J. Syph., Gonor. & Ven. Dis. **30**:125 (March) 1946.

30. Tello, E. E.: Sífilis primaria de cuello de útero en la mujer no embarazada, Thesis for the Doctorate, Cordoba, University of Cordoba, 1945.

31. Hazen, H. H.: Extragenital Syphilitic Infection in Negroes, Arch. Dermat. & Syph. **52**:114 (Aug.) 1945.

19 of 3,700 Negro patients with early syphilis had extragenital chancres, a percentage of 0.51. This is about 1/10 the reported percentage among white patients.

Electrocardiographic Changes in Early Syphilis. — Whether the spirochetes which lodge in the cardiac muscle during the spirochetemia of early syphilis cause any demonstrable alteration in cardiac function has been the subject of conflicting opinions. Klotz and Crede [32] found definite electrocardiographic changes (abnormally shaped T waves) in 4 of 100 patients with early syphilis, which became normal after a twenty day course of arsenotherapy. Six additional patients showed low voltage T waves, which increased in amplitude following the completion of treatment. Other findings noted in isolated instances were low voltage with some slurring of the initial complexes, slight depression of the S-T segments, ectopic ventricular premature systoles and a shifting pacemaker, all of which disappeared following therapy. The authors feel that the electrocardiographic changes observed indicate that myocardial damage may occur in early syphilis.

Relapse and Reinfection.

As Moore [33] states editorially in the *American Journal of Syphilis, Gonorrhea and Venereal Diseases,* the problems of reinfection, superinfection and relapse have assumed far greater importance since the advent of intensive arsenical and penicillin therapy. Even with rigid criteria, reinfection appears now to be from five to ten times as common as in previous years. In a critical analysis, it is pointed out that newer methods of treatment have made invalid several of the previously proposed criteria of reinfection, leaving little evidence on which to differentiate among reinfection, superinfection and infectious relapse, save alone clinical "impressions" or diagnostic "hunches," which do not constitute proof. There are reasons, based primarily on experimentation with animals but also on recent clinical observations, to discard the concept that reinfection is proof of cure. If this concept is incorrect, superinfections and reinfections may well be more frequent than is commonly supposed. To the individual patient, the subject is of academic interest only, since whether he is reinfected, superinfected or relapses he must be retreated. To physicians attempting to evaluate accurately new and rapidly effective schedules of treatment, it is of practical importance. As more precise methods of effecting a differentia-

32. Klotz, S. D., and Crede, R. H.: Electrocardiographic Changes in Early Syphilis Prior to and upon Completion of Intensive Arsenotherapy, Am. Heart J. **30**:551 (Dec.) 1945.

33. Moore, J. E.: The Changing Concept of Reinfection with Syphilis and Its Applicability as a Criterion of Cure, editorial, Am. J. Syph., Gonor. & Ven. Dis. **29**:474 (July) 1945.

tion are lacking, it is unfortunately necessary to designate all supposed reinfections as "treatment failures."

Noting that wholesale reports of so-called reinfections have followed the introduction into syphilotherapy of new and supposedly "curative" procedures, Beerman [34] enjoins caution in relaxing the rigidity of criteria for proof of reinfection. He bases much of his discussion on an extensive review of the literature pertaining to the problem of human reinoculations with T. pallidum. Thomas, Wexler and Schur [35] have observed a patient with cardiovascular syphilis (aortic regurgitation) in whom, having been treated to the point of seronegativity, there developed ten years after treatment for his original infection a dark field–positive chancre of "superinfection." The alternate explanation is, of course, that after cure of the original infection and gradual dissolution of whatever immunity it may have engendered the patient was reinfected.

Ocular Syphilis.

Interstitial Keratitis.—Woods and Chesney [36] summarize the results of an extensive series of experiments on the relation of the eye to immunity to syphilis, in which they found that (*a*) the corneas of rabbits with experimental syphilis induced by intratesticular inoculation do not always share in the immunity to reinfection which develops during the course of syphilitic infections; (*b*) direct inoculation of the cornea is followed by the development in that tissue of a local resistant state, although in some instances the protection thus conferred either is not absolute or is not permanent, and (*c*) vascularization of the cornea appears to be a factor in influencing favorably the development of a local resistant state.

The authors discuss the bearing of their findings on the pathogenesis of interstitial keratitis. It is suggested that the usual late occurrence of the lesions of interstitial keratitis may be due to a combination of lack of local immunity in the cornea in some cases of congenital syphilis plus the occurrence of minor traumatic incidents as the initiating factor. The fact that the lesions of interstitial keratitis may heal spontaneously as vascularization occurs may be explained on the basis of the development of a local immunity, presumably through antibodies

34. Beerman, H.: The Problem of Reinoculation of Human Beings with Spirochaeta Pallida: A Review of the Literature, Am. J. Syph., Gonor. & Ven. Dis. **30**:173 (March) 1946.

35. Thomas, E. W.; Wexler, G., and Schur, M.: Report of a Chancre Developing in a Patient with Cardiovascular Syphilis, Am. J. Syph., Gonor. & Ven. Dis. **29**:604 (Nov.) 1945.

36. Woods, A. C., and Chesney, A. M.: Relation of the Eye to Immunity in Syphilis with Special Reference to the Pathogenesis of Interstitial Keratitis, Am. J. Ophth. **29**:389 (April) 1946.

present in the blood. The tendency of the lesions of interstitial keratitis to recur may be related to the fading of a local immunity.

Syphilitic Uveitis.—The difficulties in establishing the diagnosis of syphilitic uveitis and in evaluating the results of therapy are discussed by Klauder and Dublin,[37] who report a series of 72 cases. These authors point out that neither clinical appearances, positive serologic reactions for syphilis, occurrences of Herxheimer reactions nor responses to antisyphilitic treatment are infallible criteria in the diagnosis of syphilitic uveitis. Clinically there are no features of serous or plastic iritis pathognomonic of syphilis. The nodular type, while somewhat more characteristic, may be confused with iritis due to such other causes as tuberculosis, sympathetic ophthalmitis, sarcoidosis, leukemia, leprosy and neoplasm. The occurrence of Herxheimer reactions was studied with the corneal microscope and the slit lamp before and after therapy. This reaction was observed in 70 per cent of 65 patients with early syphilitic uveitis and in all of 7 patients whose only other evidence of syphilis was a positive serologic reaction. Since, however, 9 of 36 patients (25 per cent) with uveitis unassociated with clinical evidence of syphilis also had transient intensification of the inflammatory reactions following therapy, the authors do not believe that the occurrence of a Herxheimer reaction following therapy constitutes an absolute criterion in differential diagnosis.

The therapeutic response of syphilitic uveitis was good. Not only did the acute inflammation subside, but visual acuity seemed fairly well preserved. In only 1 patient was the outcome inadequate for industrially useful vision. Secondary glaucoma occurred in 3 cases. Seventeen patients with uveitis associated with early syphilis were treated with penicillin in a total dosage of 2,400,000 units. Penicillin had a prompt effect on the ocular lesion. Inflammation disappeared in from eight to fourteen days after the first injection in all but 2 patients, and no ocular relapse was observed during the period of observation.

The authors point out, however, that antisyphilitic treatment may exert a nonspecific effect on inflammatory processes of the uveal tract. Furthermore, syphilitic iritis may heal in the absence of treatment. In the authors' experiences, the beneficial nonspecific effect of antisyphilitic treatment was not uniform nor was it always lasting. Since a definite diagnosis of syphilitic uveitis cannot be made clinically and since histologic examination or dark field demonstration of T. pallidum is not feasible, Klauder and Dublin state the belief that the diagnosis is established by evaluating all available data, the most important criteria

37. Klauder, J. V., and Dublin, G. J.: Syphilitic Uveitis: Diagnosis, Herxheimer Reaction and Results of Various Treatments, Including Penicillin Therapy, Arch. Ophth. **35**:384 (April) 1946.

being (1) evidence of recent infection with syphilis, (2) the exclusion of other possible etiologic factors and (3) a prompt response to antisyphilitic treatment.

Aural Syphilis.

Rodger [38] has recorded his observations on aural syphilis, drawn from 500 cases of syphilis involving the ears, nose and throat. His speculations as to the site of the lesion in the various types of deafness occurring in congenital and acquired syphilis are undocumented by pathologic evidence; his statement that syphilis causes diseases of the middle ear will not be accepted by most experienced otologists and syphilologists, and his discussion of the results of treatment in syphilitic cochlear and vestibular disease is worthless.

Cardiovascular Syphilis.

Uncomplicated Aortitis.—The successful clinical diagnosis of uncomplicated syphilitic aortitis depends on the alertness and clinical acumen of the examiner as well as the extent of the pathologic process. That this condition frequently is overlooked is readily apparent from the discrepancy between its incidence in clinical and pathologic reports. Dressler [39] has studied 1,270 patients with syphilis in an effort to seek criteria that permit a diagnosis of uncomplicated aortitis. In this series, a clinical diagnosis of cardiovascular syphilis was made in 30.7 per cent of the cases. Of the patients with conditions so diagnosed, 78 per cent were considered to have uncomplicated aortitis. To the author, the results of his study suggest that uncomplicated aortitis is a symptomless condition. The following criteria are suggested for establishing a diagnosis of aortitis in patients under 40 years of age: (1) the presence of a typical aortic second sound, (2) suprasternal pulsations, (3) increased paramanubrial dulness in the second intercostal space, (4) hypertension and (5) fluoroscopic evidence of aortic dilatation.

Aneurysms of the Thoracic Aorta.—Uncomplicated syphilitic aneurysm of the thoracic aorta imposes little or no appreciable strain on the heart. When congestive cardiac failure supervenes, it is oftenest the result of involvement of the aortic valve or of narrowing of the coronary ostiums. In either instance, the strain is predominantly on the left ventricle.

A rarer complication of aortic aneurysm, discussed by Brill and Jones,[40] is compression of the pulmonary artery, with or without arterio-

38. Rodger, T. R.: Aural Syphilis, Brit. J. Ven. Dis. **21**:115 (Sept.) 1945.

39. Dressler, M.: Cardiovascular Syphilis: An Approach to Early Clinical Recognition and Early Treatment, Connecticut M. J. **9**:844 (Nov.) 1945.

40. Brill, I. C., and Jones, R. S.: The Syndrome of Compression of the Pulmonary Artery by a Syphilitic Aortic Aneurysm With or Without Arterio-Arterial Communication, Ann. Int. Med. **24**:111 (Jan.) 1946.

arterial communication. In this instance, the strain is predominantly on the right ventricle. The authors suggest that when severe cardiac failure on the right side supervenes in a case of syphilitic aneurysm of the thoracic aorta without other discernible complications to account for the congestive failure compression of the pulmonary artery should be suspected. Arterioarterial communication is indicated by the presence of a continuous machinery type of murmur in the area of the pulmonary valve similar to that frequently observed in patent ductus Botalli.

A number of procedures have been advocated for producing occlusion of large blood vessels. In addition to the ineffectual results and fatal complications that attend many of these methods almost all are too traumatic for application to a thin-walled syphilitic aneurysm of the aorta. The methods of occlusion may be classified as follows: (1) the insertion of foreign bodies into the lumen of the vessels to produce thrombosis (Blakemore [41]), (2) external compression of the vessel and (3) injuries to the wall of the vessel, resulting in fibrosis and constriction of the lumen.

Poppe and de Oliveira [42] report the successful use of applications of polythene cellophane to fibrous and obliterate syphilitic aneurysms of the thoracic aorta. Preliminary experimental data indicated that polythene cellophane was superior to other types and that the method was surgically feasible in dogs. The authors have successfully treated aneurysms of the aorta and have obliterated a patent ductus arteriosus by the method.

Neurosyphilis.

Asymptomatic Neurosyphilis.—Merritt [43] found asymptomatic neurosyphilis to be present in 9.5 per cent of 2,263 patients with syphilis of five or more years' duration. An analysis of 676 cases of neurosyphilis of all types showed that asymptomatic neurosyphilis constituted 32 per cent of the total. The latter group of 200 cases of asymptomatic neurosyphilis is discussed in detail. In 8 per cent of the 200 patients there developed clinical evidence of progression following therapy. In no patient with minimal pretreatment abnormalities of the spinal fluid did the condition progress to parenchymatous neurosyphilis, and in only 4 per cent did lesions of the meningovascular type develop. On the other hand, parenchymatous neurosyphilis developed in 20 per cent of the patients with fluids of the group III type.

41. Blakemore, A. H.: Electrothermic Coagulation of Aneurysms, in Nelson Loose-Leaf Medicine, New York, Thos. Nelson & Sons, 1945, chap. 12-B.

42. Poppe, J. K., and de Oliveira, H. R.: Treatment of Syphilitic Aneurysms by Cellophane Wrapping, J. Thoracic Surg. **15**:186 (June) 1946.

43. Merritt, H. H.: Asymptomatic Neurosyphilis, Clinics **4**:475 (Aug.) 1945.

Dementia Paralytica (Palmomental Reflex in).—Thompson [44] reports that the palmomental reflex has a high degree of specificity in dementia paralytica, is one of the first physical signs to appear and is present "in almost 100 per cent of cases of this disorder." The palmomental reflex is elicited by stroking with a moderately sharp instrument the thenar eminence from the base of the thumb to the wrist. As the stroke is made, the examiner watches the ipsilateral side of the patient's chin. A positive sign is elicited when the skin just lateral to the midline of the chin forms a dimple and moves laterally and upward. The sign oftenest is ipsilateral, but it may be contralateral and occasionally bilateral. The significance of the sign is its frequency of occurrence in diseases causing diffuse cortical damage. A positive palmomental sign occurs in about 2 to 3 per cent of normal persons. Among the diseases in which the sign occurs are multiple sclerosis, lethargic encephalitis, other forms of neurosyphilis, cerebral arteriosclerosis, severe alcoholic mental deterioration and opium addiction with mental deterioration. In none of these is it as consistently present as in dementia paralytica.

Syphilitic Amyotrophy.—So common is muscular atrophy in the course of tabes dorsalis that it is generally accepted as one of the predominant signs of the condition. Extremely controversial, however, is the relationship of syphilis to neurologic syndromes such as chronic poliomyelitis, amyotrophic lateral sclerosis and the muscular dystrophies.

Revilla [45] describes 7 patients with syphilis in whom the outstanding objective findings were those of amyotrophy and in whom he believes the etiologic factor was syphilis. Pain was a predominant symptom, in contrast to idiopathic amyotrophic lateral sclerosis, which ordinarily is painless. Certain other clinical differences were observed: the muscular atrophy was asymmetric and irregular in distribution; deep reflexes usually were hypoactive, although occasionally hyperactive; pupillary abnormalities were frequent, and the clinical course was more protracted and less consistently progressive than that in the idiopathic type of amyotrophy.

Antisyphilitic therapy appears to influence the course of the muscular dystrophy but little. Even fever therapy is ineffectual, reports Vraa-Jensen,[46] who has treated 6 patients with "amyotrophic cerebrospinal syphilis" with the Kettering hypertherm.

Avitaminosis and Syphilis of the Spinal Cord.—In recent years there has been considerable investigation of the neuropathologic changes pro-

44. Thompson, G. N.: The Palmo-Mental Sign, Bull. Los Angeles Neurol. Soc. **10**:174 (Sept.-Dec.) 1945.

45. Revilla, A. G.: Syphilitic Amyotrophy: Clinical Study of Seven Cases, Dis. Nerv. System **7**:69 (March) 1946.

46. Vraa-Jensen, G.: Amyotrophic Cerebrospinal Syphilis, Acta psychiat. et neurol. **21**:795, 1946.

duced by avitaminosis. Shulack and Peters' review [47] of the present status of these investigations reveals degeneration of the posterior columns of the spinal cord to be the commonest manifestation of long-standing vitamin deficiency. Less often the lateral columns show degenerative changes.

Heilbrunn and Hoffenberg [48] have treated 15 patients with various neurologic disorders with oral administration of vitamin B complex and vitamin E and intrathecal injection of crystalline thiamine hydrochloride. Included in the group were 3 patients with tabes dorsalis, 2 of whom showed symptomatic improvement (in ataxia and sensory disturbances).

Electroencephalograms in Neurosyphilis.—Greenblatt and Levin [49] have found electroencephalographic abnormalities in 50 per cent of 233 cases of neurosyphilis. The incidence of abnormality in the various clinical types was meningovascular neurosyphilis, 60 per cent; dementia paralytica, 55 per cent, and tabes dorsalis, 14 per cent. In a control group, the incidence of abnormality was 10 per cent.

Twenty per cent of the patients with neurosyphilis had histories of convulsive attacks. The highest incidence of convulsions was among patients with meningovascular involvement, attacks also being common among those with dementia paralytica. Abnormal electroencephalograms were especially frequent among patients with a history of seizures.

In the group of persons with dementia paralytica, various clinical and laboratory findings were correlated with the incidence of abnormality of electroencephalograms. The presence of tremors, dysarthria and other somatic signs raised the incidence of electroencephalographic abnormality. The degree of spinal fluid abnormality and the presence of evidence of "activity" showed a slightly positive correlation. No correlation was apparent between electroencephalographic abnormality and pupillary changes or the presence of delusions or hallucinations. Of considerable interest is the finding that electroencephalographic abnormalities are frequent in cases of primary optic atrophy. This unexplained observation has previously been reported.[50]

In the neurosyphilis clinics of the Boston Psychopathic Hospital,[51] 44 of 223 patients with heterogeneous syphilis of the nervous system

47. Shulack, N. R., and Peters, M.: Spinal Cord Changes with Avitaminosis, J. Nerv. & Ment. Dis. **102**:359 (Oct.) 1945.

48. Heilbrunn, G., and Hoffenberg, N.: Intrathecal and Oral Vitamin Therapy in Various Neurologic Disorders, J. Nerv. & Ment. Dis. **102**:379 (Oct.) 1945.

49. Greenblatt, M., and Levin, S.: Factors Affecting the Electroencephalogram of Patients with Neurosyphilis, Am. J. Psychiat. **102**:40 (July) 1945.

50. Finley, K. H.; Rose, A. S., and Solomon, H. C.: Electroencephalographic Studies on Neurosyphilis, Arch. Neurol. & Psychiat. **47**:718 (May) 1943.

51. Greenblatt, M., and Levin, S.: Neurosyphilis, Convulsions and Electroencephalography, Urol. & Cutan. Rev. **50**:331 (June) 1946.

were known to have had epileptiform attacks. Of these patients 35 had dementia paralytica, and the remaining 9 had meningovascular neurosyphilis. Grand mal seizures were predominant, although focal convulsions were commoner in cases of meningovascular disease. There were no instances of petit mal. Approximately half of these 223 patients had electroencephalographic abnormalities, and the authors claim a correlation of these abnormalities with the incidence of epileptiform attacks. In their experience, the more abnormal the electroencephalogram, the greater the likelihood of the patient's having a history of convulsions. In a comparison of seizures in cases of neurosyphilis with seizures to the "general population," it was found that there is a greater number of slow wave abnormalities among the patients with neurosyphilis than among patients wth so-called idiopathic epilepsy.

Abnormalities of Spinal Fluid.—The spinal fluid syndrome characterized by a negative Wassermann reaction and "first zone" colloidal reaction is found, according to Rouquès,[52] almost invariably in cysticercosis and trypanosomiasis, not infrequently in multiple sclerosis but only rarely in neurosyphilis.

Lumbar Puncture.—Following lumbar puncture there may occur a syndrome consisting of headache, varying in intensity and duration, nausea, vertigo, backache and stiffness of the neck. Characteristically, the headache is relieved by recumbency and aggravated by activity. The mechanism of this postpuncture reaction has been extensively discussed but never completely elucidated.

In Underwood's[53] experience, lumbar puncture was followed by temporarily incapacitating headache in 19 per cent of 500 cases. Postpuncture reactions were more frequent among patients whose spinal fluids were normal than among those with neurosyphilis. Other predisposing factors appeared to be initially low spinal fluid pressure, emotional reactions to the examination and a history of previous reactions to the procedure. Rest in bed following a lumbar puncture did not reduce the incidence of headache. Indeed, the evidence presented suggests that postpuncture recumbency increases not only its frequency but also its duration. Fifteen per cent of the group who did not rest and 25 per cent of those who rested after the procedure had moderate to severe reactions. Among those who returned to work immediately and in whom symptoms developed, 56 per cent of the headaches lasted three to five days; whereas in the group who remained recumbent, 60 per cent persisted three to seven days. Severe reactions lasted more

52. Rouquès, L.: Des réactions du Benjoin colloïdal et de Wassermann dans le liquide céphalo-rachidien, Presse méd. **54**:427 (June 29) 1946.

53. Underwood, L. J.: Lumbar Puncture Headache: A Statistical Analysis of Five Hundred Punctures, Am. J. Syph., Gonor. & Ven Dis. **30**:264 (May) 1946.

than three days in 97 per cent and longer than five days in 36 per cent of the cases. One severe headache persisted for over six weeks. For extreme postpuncture reactions, rest in bed for twenty-four to forty-eight hours and the use of caffeine and sodium benzoate intravenously are recommended.

In their report of the use of sodium nicotinate given intravenously in the treatment of various types of headache, Goldzieher and Popkin [54] record that complete relief was afforded each of 13 patients with post-lumbar puncture headache. The dosage given was 100 mg. of nicotinic acid or its equivalent as the sodium salt. This form of therapy was not without discomfort, for the injections were followed by a "burning" sensation and flushing, restlessness, oppression and paresthesias. The relief of headache appeared to be correlated with the degree of peripheral flush.

Lumbar puncture as a diagnostic procedure seldom is attended by any untoward sequelae other than headache, but in rare instances neurogenic disturbances may occur. Robinson [55] has reported transient paralysis of the abducens nerve five days following this procedure. Rangell and Glassman [56] add acute spinal epidural abscess to the list of possible complications following routine lumbar puncture. This, which fortunately is extremely rare, usually consists in the following sequence of events: (1) severe pain in the root, the distribution depending on the level of the lesion; (2) a latent period, usually four to nine days in duration, followed by signs of compression of the spinal cord; (3) evidence of cord involvement, manifested by motor paralyses, hypesthesia and sphincter disturbances; (4) fever, tachycardia, leukocytosis and other signs of severe infection, and (5) localized tenderness and rigidity of the spine, with obvious inflammation of the paravertebral muscles and soft tissues. The epidural space is composed of a meshwork of fatty and loose areolar tissue. It is oftenest infected via the hematogenous route but may be involved as a result of a direct extension from contiguous disease. The staphylococus usually is the causative bacterium. Adequate surgical evacuation of the pus and open drainage are advised.

The Pathology of Syphilis.

In a continuation of his critical and statistical analysis of histopathologic changes in syphilis, Rosahn [57] compares two groups of patients

54. Goldzieher, J. W., and Popkin, G. L.: Treatment of Headache with Intravenous Sodium Nicotinate, J. A. M. A. **131**:103 (May 11) 1946.

55. Robinson, H. J., Jr.: Abducens Palsy (with Subsequent Recovery) Following Lumbar Puncture, Am. J. Syph., Gonor. & Ven. Dis. **29**:422 (July) 1945.

56. Rangell, L., and Glassman, F.: Acute Spinal Epidural Abscess as a Complication of Lumbar Puncture, J. Nerv. & Ment. Dis. **102**:8 (July) 1945.

with syphilis, those seronegative and those seropositive, as to the frequency of fibrosis and round cell infiltration, described by Warthin as pathognomonic of syphilitic infection. The incidence of these lesions in the heart, pancreas, adrenal, liver and testis was not significantly different in the two groups. Moreover, syphilitic patients with typical "Warthin lesions" in multiple organs were no more likely to present positive serodiagnostic reactions than those with similar lesions in only one organ. The findings indicate that the changes described by Warthin are not related to the serum reactivity to serologic tests for syphilis.

Studying the bone marrow in 40 cases of syphilis, Dulanto Escofet [58] found evidence of a shift to the left in the myelocytic series and an increase in cells of the reticuloendothelial series. A close parallelism between serum globulin fractions associated with reagin formation and the number of plasma cells in the marrow was noted.

The Prognosis of Syphilis.

Information has long been sought concerning the effect of syphilis on the life expectancy of the infected person and the influence of treatment in improving the prognosis as to life expectancy.

As Schamberg [59] points out in an extensive critical review of the available clinical, postmortem and actuarial studies, four methods of study of the prognosis of syphilis have been used: (1) analysis of governmental mortality reports, (2) clinical studies, (3) death and autopsy studies and (4) life insurance studies. Older studies were found to be untrustworthy because of factors of selection and the inclusion of conditions now known to be unrelated to syphilis. In addition, the relative ineffectiveness of older forms of therapy and the general lack of treatment facilities make invalid conclusions reached in the past, when modern forms of treatment were not available.

Analyses of governmental mortality reports are unacceptable even as gross approximations; clinical studies ordinarily are weighted to an unknown but probably considerable extent with patients with serious late lesions whose life expectancy already is foreshortened, and postmortem studies miss many cases in which the lesions have healed. In studies of American life insurance, the increased prevalence of syphilis in lower socioeconomic groups with a higher death rate introduces the major distortion. Misstatements on death certificates, inaccurate criteria

57. Rosahn, P. D.: Studies in Syphilis: VI. Fibrosis and Round Cell Infiltration of the Parenchymatous Organs (Warthin) in Relation to Serodiagnostic Findings, J. Ven. Dis. Inform. **27**:126 (May) 1946.

58. Dulanto Escofet, F.: El mielograma en la sífilis, An. méd. de Barcelona **32**:531 (Dec.) 1945.

59. Schamberg, I. L.: The Prognosis of Syphilis, Am. J. Syph., Gonor. & Ven. Dis. **29**:529 (Sept.) 1945.

of cure and adequacy of treatment and the effect of geographic residence are other factors.

The presumed increased mortality rate among syphilitic persons may be ascribed to two causes: (1) deaths directly resulting from syphilis, chiefly from late involvement of the cardiovascular and central nervous systems and occasionally as a result of treatment (since adequate early treatment prevents the serious late manifestations, deaths directly resulting from syphilis are inversely proportional to the adequacy of treatment) and (2) the higher mortality from all causes in socioeconomic, occupational and, in some cases, geographic groups in which syphilis is most prevalent.

Schamberg states the belief that, in view of the improving standards of present day diagnosis and treatment of syphilis and in view of the frequently benign character of the disease, life insurance companies could insure at standard rates the majority of syphilitic applicants for insurance without risk of increased death losses.

Even in view of the defects inherent in any analysis utilizing governmental mortality reports, it is possible to visualize, as has Usilton,[60] certain gross mortality trends in syphilis over a period of years. Utilizing data published by the Bureau of Census, this statistical analyst found that between 1939 and 1943 there were decreasing numbers of deaths reportedly "due to syphilis," and between 1910 and 1943 there were impressive declines in the number of deaths due to dementia paralytica and those due to tabes dorsalis. In the case of dementia paralytica, significant decline did not begin until 1923, a fact which may well be related to the fact that malaria therapy came into extensive use at about this time. Perhaps most striking is the progressive decline in the infant death rate over the ten year period 1933 to 1943.

The importance of maternal syphilis as a cause of premature delivery has been difficult to assess, because of several factors that influence the interpretation of the data. Among these are the amount of antisyphilitic therapy the patients have received and the possibility of coexistent diseases which also may induce premature labor. Brown, Lyon and Anderson[61] have found, in the course of an extensive study of the causes of prematurity, that premature delivery occurred in approximately 5 per cent of mothers with normal pregnancies and in 10 per cent of those with syphilis. Antisyphilitic therapy administered during pregnancy significantly reduced the rate of prematurity.

60. Usilton, L. J.: Mortality Trends for Syphilis, J. Ven. Dis. Inform. **27**:47 (Feb.) 1946.

61. Brown, E. W.; Lyon, R. A., and Anderson, N. A.: Causes of Prematurity: V. Influence of Syphilis on the Incidence of Prematurity, Am. J. Dis. Child. **70**: 318 (Nov.-Dec.) 1945.

Heller and Bruyere [62] found that among Negro men between 25 and 50 years of age with untreated syphilis the life expectancy was about 20 per cent less than that among a comparable uninfected population. How significantly even a relatively small amount of antisyphilitic therapy may change the prognosis may be inferred by comparing this with Smith and Bruyere's [63] results, which indicate that in a population of the same age, race and sex who were infected with syphilis and received "some" treatment the life expectancy was reduced only 10 to 12 per cent below that of the general population.

DRUGS: MERCURY, BISMUTH AND ARSENICAL

Mercury.

In modern syphilology, mercurial compounds have been abandoned. The usefulness of mercury now resides solely in the fact that the local application of ointment of mild mercurous chloride is still the most effective form of chemical prophylaxis. Fleming and Wolf [64] have carried out an experiment with rabbits to evaluate the effect of particle size on the efficacy of ointment of mild mercurous chloride in the prophylaxis of syphilis. For this purpose three ointments containing mild mercurous chloride powder in particle sizes of 100 microns, 5 microns and 1 micron were used. Varying amounts of each of the three ointments were applied to the areas of inoculation one hour after standardized dark field–positive testicular emulsions had been rubbed into a superficial cutaneous scratch on each rabbit's back. Proof of protection or the lack of it was obtained by careful observation of the rabbits for chancre formation and, with clinically normal animals, by transfer of popliteal lymph nodes six months later. Their data show that greater protection was obtained with the ointments of smaller-sized particles, the particle size of 100 microns being relatively inefficacious.

Bismuth Preparations.

Vedrov [65] points out that bismuth is best absorbed during the first course of treatment, before local tissue sclerosis and vascular thrombosis resulting from previous injections have occurred. How greatly

62. Heller, J. R., Jr., and Bruyere, P. T.: Untreated Syphilis in the Male Negro: II. Mortality During Twelve Years of Observation, J. Ven. Dis. Inform. **27**:34 (Feb.) 1946.

63. Smith, D. C., and Bruyere, M. C.: The Effect of Treated Acquired Syphilis on Life Expectancy, J. Ven. Dis. Inform. **27**:39 (Feb.) 1946.

64. Fleming, W. L., and Wolf, M. H.: The Relative Prophylactic Effectiveness Against Syphilis of Ointments Containing Calomel in Different Particle Size, Am. J. Syph., Gonor. & Ven. Dis. **30**:47 (Jan.) 1946.

65. Vedrov, N. S.: Bismuth in the Treatment of Syphilis, Am. Rev. Soviet Med. **3**:106 (Dec.) 1945.

previous trauma interferes with absorption is indicated by an experiment on rabbits. A comparison was made of the bismuth content of muscles into which Biochinol (quinine bismuth iodide in peach kernal oil) was injected (*a*) one month after trauma produced by the injection of 1 cc. of pure peach kernel oil once every six days for eight injections and (*b*) when not previously traumatized. Approximately 70 per cent of the bismuth injected into undamaged muscles had been absorbed after a ten day period, while in the injured muscles the amount absorbed during the same period was only 34 per cent.

The author also studied in human patients the elimination of bismuth in urine (*a*) after one injection of Biochinol; (*b*) during one course of treatment and after its completion, and (*c*) during a repeated course of treatment and after its completion. There was a significant difference in the amount of bismuth excreted in the urine during the first course of therapy and during subsequent courses. Elimination during later series of treatment was 14 per cent of the amount injected, as compared with 32 per cent during the first course.

Arsenical Drugs.

In studying the trypanocidal and spirocheticidal activity of a series of acid-substituted phenyl arsenoxides, Eagle [66] was able to correlate therapeutic effectiveness with increasing hydrogen ion concentration within the p_H range of 5.5 to 9.0. This was due to the fact that ionized salts of the various compounds were far less active than the undissociated free acids, which had a uniform molar activity approximating that of unsubstituted phenyl arsenoxide. The relative ineffectiveness of the salts of the acid-substituted phenyl arsenoxides therefore reflects the fact that they are not bound by the organisms. Variations in p_H, affecting the ion-free acid ratio, affected the degree to which a given arsenical was bound by the organisms.

Toxic Effects of Arsenical Compounds.—The most recent analyses of Navy reports [67] indicate how much less frequent are serious untoward reactions from oxophenarsine hydrochloride than from neoarsphenamine. In a twenty year period, 1,392,838 injections of neoarsphenamine have been given, with 1,034 reactions, including 54 fatalities reported, a ratio of 1 death to every 25,793 injections. With 1,006,951 injections of oxophenarsine hydrochloride, there have been 173 reactions.

66. Eagle, H.: The Spirocheticidal and Trypanocidal Action of Acid-Substituted Phenyl Arsenoxides as a Function of p_H and Dissociation Constants, J. Pharmacol. & Exper. Therap. **85**:265 (Nov.) 1945.

67. Burton, O. L.; Justyn, G. W., and Anderson, L. T.: Toxic Effect of Arsenical Compounds, U. S. Nav. M. Bull. **45**:783 (Oct.) 1945; Toxic Effects of Arsenical Compounds, as Employed in the Treatment of Diseases in the United States Navy, 1944, ibid. **46**:139 (Jan.) 1946.

only 6 of which were fatal, a ratio of 1 death to every 167,825 injections. The six deaths due to oxophenarsine hydrochloride were two from toxic encephalopathy and one each from hepatic damage, acute renal damage, hemorrhagic encephalitis and circulatory collapse. Arsenical dermatitis was the most frequently reported reaction. These Navy data do not reflect the mortality rate from intensive arsenotherapy with either drug.

Blood dyscrasias following arsenical therapy are grave complications. Repeatedly described have been aplastic anemia, agranulocytosis and thrombocytopenia, all manifestations of depressed activity of bone marrow. The report of a case of Young, Valentine and Howland,[68] in which death followed the fifth injection of neoarsphenamine, indicates that acute hemolytic anemia also may occur as a complication of arsenical therapy and that hemolytic jaundice should be included among the possible causes of postarsenical icterus.

Larsen [69] states the belief that hemorrhagic encephalitis is due to an allergic reaction to arsenical therapy. To support his contention, he points out, among other things, that this reaction is of rare occurrence, that even small doses may evoke the complication, that most of these reactions occur early in the course of therapy and that histopathologic studies are constant with the hypothesis.

Colloidoclastic shock following the injection of oxophenarsine hydrochloride is rare. In Shapiro's [70] patient, treated for blastomycosis rather than for syphilis, there developed ashen pallor, apnea and circulatory collapse following the second injection. Recovery was prompt.

Conrad [71] adds to the list of eruptions reported following the use of oxophenarsine hydrochloride a fixed dermatitis with pemphigoid features.

In reporting 2 cases of acute agranulocytosis, 1 with coexisting toxic hepatitis attributable to therapy with oxophenarsine hydrochloride, McManus [72] indicates that penicillin was of distinct value both as prophylaxis against the usually fatal septicemia which commonly develops and as therapy for the underlying syphilitic infection.

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68. Young, L. E.; Valentine, W. N., and Howland, J. W.: Acute Hemolytic Anemia Due to Neoarsphenamine: Report of a Fatal Case, Ann. Int. Med. **24**: 104 (Jan.) 1946.

69. Larsen, J. F.: Encephalopathia allergica e neosalvarsano, Acta psychiat. et neurol. **21**:473, 1946.

70. Shapiro, A. L.: Colloidoclastic Shock Following Injection of Oxophenarsine Hydrochloride (Marpharsen), Arch. Dermat. & Syph. **52**:395 (Nov.-Dec.) 1945.

71. Conrad, A. H., Jr.: Fixed Arsenical Eruption with Bulla Formation, Bull. U. S. Army M. Dept. **5**:726 (June) 1946.

72. McManus, J. F.: Agranulocytosis Following Mapharsen Therapy, New England J. Med. **234**:17 (Jan. 3) 1946.

Walsh and Wyatt [73] have observed the results of accidental intra-arterial injection of oxophenarsine hydrochloride. Severe pain distal to the point of injection, generalized in the forearm and hand but severest in the thenar and hypothenar eminences and in the finger tips, occurred immediately and persisted for several hours. There were no serious sequelae.

Leifer [74] stresses the danger of continued arsenotherapy in cases of "erythema of the ninth day." He reports 14 cases of this reaction occurring early in the course of arsenotherapy (from six to eleven days after the first injection). All patients had fever, headache and weakness, but only 3 had cutaneous eruptions. In all, early continuation of arsenical drugs after the initial reaction caused serious reactions, in the form of jaundice or agranulocytosis, each often accompanied with concomitant nephritis. The author expresses the opinion that the safest course is to consider any febrile episode (except the Herxheimer reaction) in the first three weeks of arsenotherapy as a probable manifestation of arsenical sensitivity.

Arsenical Jaundice and Syringe Hepatitis.—As a reaction to antisyphilitic therapy, jaundice long has been considered unique. Its capricious occurrence (not infrequently late in the course of therapy), the facts that early resumption of arsenical therapy often is possible and that clinical differentiation from "catarrhal jaundice" is difficult and the lack of characteristic histopathologic changes in the liver all have reserved for this complication of antisyphilitic therapy a category unto itself.

It is now well recognized that hepatitis which may follow the injection of convalescent serum or of vaccines containing human serum is due to a hepatotoxic factor in the serum. This form of hepatitis, now known as "homologous serum jaundice," is indistinguishable from that which occasionally follows arsenotherapy, and there now is ample proof that in many cases "arsenical hepatitis" is in reality due to contamination of syringes with a transmissible icterogenic agent occasionally present in human serum. The problem has been the subject of several recent British publications, since in England the problem of "arsphenamine jaundice" long has been out of all proportion to the other toxic reactions associated with arsenical therapy. In a memorandum by medical officers of the British Ministry of Health [75] it is recommended that the technics of arsenical injection commonly used in England be revised. Theories that hepatitis is directly due to syphilis or that it is due to an

73. Walsh, E. N., and Wyatt, J. L.: Accidental Intra-Arterial Injection of Oxophenarsine Hydrochloride (Mapharsen), J. A. M. A. **129**:1255 (Dec. 29) 1945.

74. Leifer, W.: The Danger of Continued Arsenotherapy in Cases of Erythema of the Ninth Day, Am. J. M. Sc. **210**:458 (Oct.) 1945.

75. Role of Syringes in the Transmission of Jaundice, Lancet **2**:116 (July 28) 1945.

intercurrent infection spreading spontaneously among persons made unusually susceptible to the toxic effects of syphilis or of arsenic are rejected in view of conclusive evidence that an infective agent may be transmitted by syringes or needles.

In considering the prophylaxis of syringe hepatitis, Dalmady and Hardwick [76] stress that the quantity of icterogenic principle may be extremely small and that the agent is heat resistant and not killed by ordinary methods of sterilization. It is therefore believed essential that all syringes should be sterilized by dry heat. For routine chemical and serologic analysis, it is recommended that blood be withdrawn directly into collecting tubes, without the intermediary use of syringes.

Homologous serum jaundice has been reported following the parenteral (not necessarily intravenous) injection of insulin, gold, and bismuth preparations and acriflavine and even after the use of common syringes for venesection. As Howells and Kerr [77] point out, it also may follow injections of penicillin if proper precautions are not taken.

"BAL" Therapy of Arsenical Poisoning.—The compound dimercaprol ("BAL"; 2,3-dimercaptopropanol) was developed during the war as an antidote against arsenical blister gases. Subsequently, it was found also to be effective not only for local decontamination and treatment of the skin and eyes but also for systemic treatment of arsenic poisoning, either occurring after exposure to arsenical blister gases or observed as a complication of arsenotherapy. The brilliant experimental studies of Stocken, Thompson, Peters and their associates which led to the development of dimercaprol and the extensive studies of its biochemical and pharmacologic properties recently have been reviewed by Waters and Stock [78] and by Peters, Stocken and Thompson.[79]

Eagle [80] summarizes the pharmacologic and clinical data which indicate that dimercaprol is of value in the treatment of certain types of arsenical poisoning. The toxicity of arsenicals rests on the fact that they combine with and block the function of physiologically essential chemical groupings in the cell, specifically of cellular sulfhydryl groups. Dimercaprol competes so favorably with sulfhydryl groups in the tissue that arsenic is removed from the cells even after being bound. A

76. Dalmady, E. M., and Hardwick, C.: Syringe-Transmitted Hepatitis, Lancet **2**:106 (July 28) 1945.

77. Howells, L., and Kerr, J. D. C.: Hepatitis After Penicillin Injections, Lancet **1**:51 (Jan. 12) 1946.

78. Waters, L. L., and Stock, C.: BAL (British Anti-Lewisite), Science **102**: 601 (Dec. 14) 1945.

79. Peters, R. A.; Stocken, L. A., and Thompson, R. H. S.: British Anti-Lewisite (BAL), Nature, London **156**:616 (Nov. 24) 1945.

80. Eagle, H.: The Systemic Treatment of Arsenic Poisoning with BAL (2,3-Dimercaptopropanol), J. Ven. Dis. Inform. **27**:114 (May) 1946.

regular and sometimes striking increase in arsenic excretion follows. Studies in animals poisoned by oxophenarsine hydrochloride, lewisite (betachlorovinyldichloroarsine) or phenyl arsenoxide (arsenosobenzene) indicate that the widest margin of safety between toxic and effective doses of dimercaprol is provided by intramuscular injection (the drug dissolved in peanut oil) at four hour intervals. In human beings the therapeutic dose is approximately 3 mg. per kilogram, the number of injections depending on the severity of the complication. Larger doses may cause such untoward symptoms as nausea, vomiting, headache, a burning sensation in the lips, mouth, throat and eyes, myalgia and a sense of constriction in the chest. The results of systemic therapy with dimercaprol in cases of arsenic poisoning are summarized. Patients with toxic encephalitis, arsenical dermatitis and massive overdoses of oxophenarsine hydrochloride appear to have been benefited. In the severe complications the mortality rate apparently is reduced and the period of hospitalization shortened. In the milder complications, recovery is accelerated. The effect of dimercaprol in postarsenical blood dyscrasias and icterus is dubious. In all the reports, the importance of prompt administration of adequate amounts of dimercaprol is clearly evident.

In 55 patients with encephalopathy caused by intensive arsenotherapy, 40 were either convulsing or in coma at the time of administration of dimercaprol. Forty-four patients recovered within one to seven days, usually with improvement within one to three days; 11 died.

Eighty-eight patients with arsenical dermatitis have been treated, some systemically and some locally with dimercaprol ointments. The administration of dimercaprol usually stopped the progression of the inflammatory process. The average time for definite improvement to occur in exfoliative dermatitis was three days, and the average time for almost complete recovery was thirteen days.

In 10 of 11 cases of agranulocytosis due to arsenical therapy, administration of dimercaprol was followed by an increase in the white blood cell count and an even more striking increase in the proportion of polymorphonuclear granulocytes. The course of 3 patients with aplastic anemia was not influenced by dimercaprol in the doses used.

Three patients who were given massive overdoses of oxophenarsine hydrochloride and who received prompt and adequate amounts of dimercaprol recovered. A fourth patient received inadequate amounts of dimercaprol and died after an initially favorable response.

In 6 normal subjects, in 12 volunteers exposed to small concentrations of arsenical smoke and in 11 patients with arsenical dermatitis, the injection of dimercaprol regularly was followed by an increased urinary excretion of arsenic. This effect was relatively short lived, disappearing within four hours after a single injection.

Dimercaprol is itself toxic. This toxicity may be related to its strong reducing properties. It can destroy hemin or oxyhemoglobin by splitting the porphyrin ring and can also reduce methemoglobin or cytochrome C. Modified formulas of dimercaprol may be expected, and already a report by Danielli and his co-workers [81] describes a glucoside of dithioglycerol ("BAL-*Intrav*"), which may prove more suitable for systemic arsenical poisoning. Intravenous injections of this glucoside in dosage of 100 mg. per kilogram have been given without toxic symptoms, whereas doses of dimercaprol in excess of 4 mg. per kilogram have caused serious untoward reactions.

Intensive Arsenotherapy.—Bowman and Humphrey [82] have treated 800 patients with early syphilis by the five day intravenous drip method. Their patients received oxophenarsine hydrochloride in total amounts from 1,000 to 1,200 mg., depending on body weight, and over 70 per cent also received intramuscular injections of thio-bismol. The outcome of treatment was considered satisfactory in 96.4 per cent of the cases of seronegative primary syphilis, in 83.9 per cent of the cases of seropositive primary syphilis and in 78.0 per cent of the cases of secondary syphilis. There were four deaths, a mortality ratio of one death in every 200 patients treated. Death was due to encephalopathy in 3 of the patients and to hepatic damage in the fourth. Three additional patients had severe but nonfatal encephalopathy.

However, Shaffer [83] reports that the five day intravenous drip method of massive arsenotherapy was abandoned because of serious reactions to treatment, results that were none too satisfactory and a lack of specially trained personnel. In its stead was substituted an ambulatory intensified treatment schedule consisting of a total of thirty injections of oxophenarsine hydrochloride and eight of bismuth subsalicylate given over a period of fifteen and two-thirds weeks. This is a compromise between the twenty-six week "Army" plan and the eight to ten week "Eagle" schedule. Two hundred and ten patients with early syphilis were assigned to this method of treatment during 1942.[83] The greatest drawback proved to be unsatisfactory case holding, since only 63 patients (30 per cent) completed the treatment with satisfactory regularity and remained under observation for six months or more.

81. Danielli, J. F.; Danielli, M.; Mitchell, P. D.; Owen, L. N., and Shaw, G.: Development of a Chemotherapy for Systemic Arsenical Poisoning, Nature, London **157**:217 (Feb. 23) 1946.

82. Bowman, G. W., and Humphrey, P. E.: Résumé of Eight Hundred Cases of Early Syphilis Treated by Five-Day, Slow-Drip Method, J. Indiana M. A. **38**:259 (Aug.) 1945.

83. Shaffer, L. W.: Intensive Arsenotherapy of Early Syphilis, Arch. Dermat. & Syph. **52**:147 (Sept.) 1945.

Of those who completed this form of therapy, 89 per cent had negative clinical and serologic results, 8 per cent were seroresistant and 3 per cent had clinical relapses. It was necessary to discontinue treatment in 7 cases because of reactions. Experiences with the eight week "Eagle" plan of intensified therapy are also given. A total of 352 patients were given three injections of oxophenarsine hydrochloride and one injection of bismuth subsalicylate per week for eight weeks. One hundred and ninety-four of these patients failed to complete this treatment. Among those whose therapy was completed there was a 10.3 per cent rate of failure (seroresistance, serorelapse or clinical relapse). Untoward reactions necessitated discontinuation of treatment for 8 patients.

Shaffer states the belief that such ambulatory intensive schedules are satisfactory for general use because of their safety, simplicity and effective results. The weakness of the method is the difficulty in holding patients to the schedule without lapses in treatment.

So acute has been the problem of lapses in the course of all but the most "intensified" of the treatment schedules that Trow and Dixon [84] have suggested that all patients be hospitalized during the entire treatment to insure its completion. However desirable this may be, it is not feasible. Hospital facilities are inadequate; the expense is too great, and social and business reasons make it impracticable to confine all patients to a hospital for antisyphilitic therapy.

Figueroa and Haraszti [85] have treated 1,000 patients with early syphilis by one of three schemes of intensive arsenotherapy. The five day intravenous drip method was used for 564 patients, and 500 (88.6 per cent) completed the treatment. Satisfactory results were obtained in 84.5 per cent of those whose therapy was completed. There were six deaths, all due to arsenical encephalopathy, a mortality rate of approximately 1 per cent. Of 186 patients treated by one of several thirty to forty day multiple syringe technics, 167 (89.8 per cent) completed treatment, with 79 per cent satisfactory results and no deaths. There were 250 patients treated by combined fever (from injections of foreign protein) and oxophenarsine hydrochloride, and 89.2 per cent completed the therapeutic course. The outcome was satisfactory in 93.8 per cent of the latter group. There were no deaths.

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84. Trow, E. J., and Dixon, H. A.: Intensive Treatment of Early Syphilis with Oxophenarsine Hydrochloride by Multiple Injections, Arch. Dermat. & Syph. **52**:155 (Sept.) 1945.

85. Figueroa, B. E., and Haraszti, S. E.: Experiencias sobre méthodos modernos de arsenoterapia en 1000 casos de sífilis reciente, Rev. med. e cir. de São Paulo **19**:3 (April) 1946.

Cannon's schedule of intensive arsenotherapy involving massive fractional doses of old arsphenamine administered by the syringe method three to four times daily over a period of from five to six days proved entirely unsuitable for the treatment of early syphilis. This die-hard attempt to retain for Erlich's "magic bullet" a place in modern syphilology has, however, enabled Cannon and his co-workers [86] to record some observations on blood and urinary levels of arsenic. The concentration of arsenic in the blood and urine was found to vary from patient to patient and from day to day throughout the period of treatment. Because of the prolonged presence of arsenic in the blood and urine following this method of administering arsphenamine, the suggestion is made that temporary retention of arsenical drugs by the body tissues may occur.

Krichevskaya and Lass [87] report finding arsenic in the cerebospinal fluid in over half of a group of 92 patients who received massive arsenotherapy by continuous intravenous drip. Meningeal inflammation, increased body temperature and high concentration of arsenic in the blood are believed to be factors in facilitating the passage of arsenic through the hematoencephalic barrier.

Untoward Reactions to Intensive Arsenotherapy: Having treated 960 patients with the administration of oxophenarsine hydrochloride by the five day continuous drip method, Bowman and Humphrey [88] report twenty cerebral reactions, eleven of which were serious and five fatal. These reactions were more frequent in women, in the white race and among patients with florid secondary syphilis. Postmortem findings usually revealed cerebral edema rather than true hemorrhagic encephalopathy

Polyneuritis is a rare complication of routine antisyphilitic therapy. It has been observed oftenest after treatment with sulfarsphenamine and commonly in association with exfoliative dermatitis. As Franks, Fetterman and Romano [89] point out, this complication has been more frequent since the introduction of more intensive methods of arsenotherapy.

86. Cannon, A. B.; Fisher, J. K.; Rodriquez, J. J.; Beattie, G. F., and Maechling, E. H.: Blood and Urine Arsenic Levels of Patients with Early Syphilis Under Intensive Arsenotherapy, Am. J. Syph., Gonor. & Ven. Dis. **30**:144 (March) 1946.

87. Krichevskaya, E. I., and Lass, D. I.: Permeability of the Hemato-Encephalic Barrier in Massive Arsenotherapy, Am. Rev. Soviet Med. **3**:38 (Oct.) 1945.

88. Bowman, G. W., and Humphrey, P. E.: Cerebral Reaction Following Massive Five-Day Slow-Drip Syphilo-Therapy, Urol. & Cutan. Rev. **49**:557 (Sept.) 1945.

89. Franks, A. G.; Fetterman, J., and Romano, D.: Neurologic Manifestations During Arsenotherapy for Syphilis, Urol. & Cutan. Rev. **49**:681 (Nov.) 1945.

These authors state the belief that arsenical peripheral neuropathy may be limited to a single nerve and may occur in the absence of exfoliative dermatitis.

Since the occurrence of jaundice in association with the arsenotherapy of syphilis first was reported, the arsenical drugs have been regarded as potentially hepatotoxic. Impressed by the rarity of hepatitis among their patients treated by the intensive five day method of arsenoxide administration, Thomas and Olansky [90] have sought to determine the possible toxic effects of massive arsenotherapy on the liver. Forty-nine patients treated with an intensive schedule, involving the intravenous administration of 1,200 mg. of arsenoxide over a period of five days, were tested before and after therapy with the following tests of hepatic function: measurement of plasma protein levels, cephalin flocculation test, intravenous hippuric acid test and bromsulfalein test. In none did there develop abnormal hepatic function as measured by the plasma protein levels or the excretion of bromsulfalein. Results with the cephalin flocculation test in 34 of the 49 patients indicated pretreatment subclinical hepatic damage, which usually improved following intensive antisyphilitic therapy. With the hippuric acid test, 37 per cent of the patients had abnormal hepatic function prior to therapy, and the post-treatment determinations again indicated not only the lack of further damage but actually the improvement of hepatic function. It is concluded that massive arsenotherapy does not usually produce hepatic damage. It also is suggested that in early syphilis there is active but subclinical hepatitis which responds favorably to antisyphilitic treatment.

Following the demonstration [91] of the fact that reduction in the concentration of prothrombin in the blood occurs during massive arsenotherapy, Hoffman and Kalz [92] have sought to correlate decreased prothrombin formation with impairment of other aspects of hepatic function. These investigators tested hepatic function by determining the blood prothrombin concentration, serum bilirubin levels, bromsulfalein retention and rate of hippuric acid synthesis in 22 patients with early syphilis during massive arsenotherapy. In 19, at least one of the four laboratory tests indicated impairment of hepatic function, prior to treat-

90. Thomas, L. J., and Olansky, S.: A Study of Liver Function Following Massive Arsenotherapy for Syphilis, Am. J. Syph., Gonor. & Ven. Dis. **30**:272 (May) 1946.

91. Kalz, F., and Steeves, L. C.: Decrease of Prothrombin Concentration in Massive Arsenotherapy, Am. J. Syph., Gonor. & Ven. Dis. **28**:89 (Jan.) 1944.

92. Hoffman, M. M., and Kalz, F.: Studies on Liver Function: I. Liver Function in Early Syphilis Before and During Massive Arsenotherapy, Am. J. Syph., Gonor. & Ven. Dis. **29**:596 (Nov.) 1945.

ment, although clinical evidences of hepatitis were absent. During arsenotherapy pronounced reduction of the blood prothrombin concentration occurred in 21 patients. In 10 patients, at least one of the other tests indicated impairment of hepatic function. Although the sensitive tests of hepatic function used in this study indicate that hepatic damage follows massive doses of arsenical drugs, in no instance was the damage sufficient to result in clinically recognizable signs and symptoms of hepatic disease. In patients who had a moderate degree of hepatic impairment before treatment there did not develop a severer grade of hepatic damage after therapy than there did in those whose hepatic function was normal. Function which was impaired during arsenotherapy was found to become normal within six months.

(To Be Concluded)

News and Comment

GENERAL NEWS

The Scientific Exhibit, Atlantic City Session of the American Medical Association.—At the Atlantic City Session, June 9 to 13, 1947, the American Medical Association will observe its centennial anniversary. For almost half of those hundred years—since 1899—the Scientific Exhibit has been a feature of each annual session and has developed into a short course in graduate medical instruction.

Exhibits at the 1947 Session will cover all phases of medicine. A certain amount of historical material will be included, but emphasis will be placed on the latest developments of medical science. The representative to the Scientific Exhibit from the Section on Internal Medicine is Dr. Thomas C. Garrett, 3803 Oak Road, Philadelphia.

Applications for space should be submitted as early as possible, since the closing date is Jan. 13, 1947. Application blanks may be obtained either from Dr. Garrett or from the Director, Scientific Exhibit, American Medical Association, 535 North Dearborn Street, Chicago 10.

Dr. Kendall Emerson to Attend Executive Committee Meeting of International Union Against Tuberculosis.—Dr. Kendall Emerson, managing director of the National Tuberculosis Association, will represent the voluntary tuberculosis associations of the United States when the Executive Committee of the International Union Against Tuberculosis meets in Paris November 7 to plan reorganization of the Union, activities of which were suspended during the war. He will be accompanied by Frederick D. Hopkins, executive secretary of the National Tuberculosis Association.

Measures for renewal and expansion of international relationships in the field of tuberculosis control will be discussed by the committee, which includes representatives of Great Britain, France, Poland, Belgium, Norway, Portugal, Italy and the United States. Also on the agenda is the question of cooperation with the World Health Organization of the United Nations. Proposals for financial support from member associations will be considered.

In discussing plans for American participation in the international organization, Dr. Emerson pointed out that tuberculosis has reached epidemic proportions in many parts of the world as a direct result of the war.

The Union was established in October 1920 as a "federation among the national associations and organizations engaged in the campaign against tuberculosis in the various countries of the civilized world." In countries in which there was no association, the appropriate government organization was the member agency. The purpose was to organize conferences, make studies, collect statistical information, stimulate scientific and social investigation and collect and distribute information to the members.

At the last conference of the Union in Lisbon in 1937, forty-three governments and national associations were listed as members. A conference scheduled to be held in Berlin in September 1939 was canceled by the outbreak of the war. Dr.

Emerson attended the last meeting of the Executive Committee in Paris in January 1939.

Dr. Emerson and Mr. Hopkins will attend by invitation a meeting of the Council of the National (British) Association for the Prevention of Tuberculosis in London before going to Paris.

Dr. Howard A. Rusk to Head New Department of Rehabilitation at New York University College of Medicine.—Dr. Howard A. Rusk, wartime Chief of the Army Air Forces Convalescent Services Program, has been named to head a new Department of Rehabilitation and Physical Medicine at the New York University College of Medicine.

The department will be the first of its kind in any medical college in the world, and will train all students through their medical college years in what is termed the "third phase of medical care"—preparing the patient to go from the bed to the job.

The department is an outgrowth and expansion of a division of physical medicine set up early last year as a part of the Department of Medicine under a grant of $250,000 from the Baruch Committee on Physical Medicine in 1944.

Dr. George G. Deaver, clinical professor of physical medicine, is to continue as head of the physical medicine division of the new department.

The department will cooperate closely with the City Department of Hospitals in establishing and supervising rehabilitation programs in all city hospitals. Forerunner of the programs planned for other hospitals is that of Bellevue, at which severely disabled persons have been given rehabilitation treatment and training under the direction of Dr. Deaver for the past two years. A special rehabilitation program has recently been inaugurated at Sea View Hospital on Staten Island, and plans are under way to start other special rehabilitation projects at Goldwater Memorial Hospital.

Dr. Rusk was awarded the Distinguished Service Medal in 1945, was cited by the American Academy of Physical Education and received the American Design Award for his work in rehabilitation.

He is a member of the President's Committee to study governmental medical care, the Baruch Committee on Physical Medicine, the Medical Advisory Board of the American Legion and the Executive Council of the National Council on Rehabilitation.

Brazilian Society of Cardiology.—The third annual meeting of the Brazilian Society of Cardiology was held in the city of Belo-Horizonte July 24 to 30. The official subject of discussion was "Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Chagas Disease."

The next meeting will take place during the first fortnight of July 1947, in Sao Salvador da Bahia. The official subject proposed is "Hypertensive and Rheumatic Heart Diseases."

The newly elected officers for 1946-1947 are as follows: President: Prof. Edgard Magalhaes Gomes; Vice President: Prof. Octavio Magalhaes; General Secretary: Prof. Roberto Menazes de Oliveira; Second Secretary: Prof. Rinaldo Chiaverini; Treasurer: Dr. Luiz Murgel, and Director of Archives of Cardiology: Dr. Jairo Ramos.

All correspondence should be addressed to the Society as follows: Sociedade Brasileira de Cardiologie, Av. Mem de Sa 197, Rio de Janeiro, D. F., Brazil.

Book Reviews

Synopsis of Physiology. By Rolland J. Main, Ph.D. Price $3.50. Pp. 341, illustrated. St. Louis: C. V. Mosby Company, 1946.

For the last ten years in the ARCHIVES OF INTERNAL MEDICINE there have been reviewed, from time to time, the synopses of different medical topics which have been published by C. V. Mosby Company. The ones seen have covered many subjects: heart disease, digestive disease, materia medica, pathologic chemistry, pathology, cutaneous disease, anorectal disease, syphilis and neuropsychiatry, to mention certain of them. Some have been as long as 671 pages and others as short as 302; the price has ranged, according to the size of the volume, from $3.50 to $6. On the whole, I have liked the series, my chief criticism being that the longer books were not really complete textbooks while the shorter ones attempted to compress too much subject matter into too little space.

Readers, on the other hand, appear to have appreciated the series thoroughly and particularly certain articles in it: Dr. George Herrmann's "Synopsis of Diseases of the Heart and Arteries" has been printed in three editions, for example, as has Dr. H. S. Crossen's "Synopsis of Gynecology," and the second edition of Dr. W. A. D. Anderson's "Synopsis of Pathology" has appeared recently. On the whole, therefore, C. V. Mosby Company is to be congratulated on having made popular a useful educational effort.

"Synopsis of Physiology" bids fair to assume a dignified position beside its sister publications. Physiology is discussed almost entirely as related to human beings, and the book admittedly is prepared for review purposes. It is the kind of text that a man returning to civilian life from the military will be glad to have within reach. The essentials of the subject are covered even though briefly and dogmatically, and there is a great deal of common sense, clinical medicine included, which many readers will find appetizing. The book can be recommended safely.

Annual Review of Physiology. By James Murray Luck, Editor, with an Editorial Committee. Volume 8. Price, $5. Pp. 658. California: American Physiological Society and Annual Reviews, Inc., Stanford University, California, 1946.

Twenty-five reviews written by twenty-nine authors and co-authors constitute the eighth volume of this important publication. It is 658 pages in length and contains 3,602 references. A complete author and subject index makes possible easy reference to the wealth of information contained in the work.

In addition to the subjects routinely treated, shock, aviation physiology and audition have been reviewed.

The volume, as in previous editions, is well bound and excellently printed on paper of good quality.

Those who wish to keep abreast of the progress of research in pure and applied biology will find this work indispensable.